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(54) Title: BIOCHEMICAL MARKERS OF THE HUMAN ENDOMETRIUM

(57) Abstract

Assay methods are provided for detection or quantitation of any of several proteins which are specifically produced in the endometrium in association with hyperplasia, adenocarcinoma or the proliferative phase of the endometrium. The relevant proteins have been identified by 2D gel electrophoresis with subsequent sequence identification by mass spectroscopic finger printing of tryptic digests.

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BIOCHEMICAL MARKERS OF THE HUMAN ENDOMETRIUM

The endometrium is the mucous lining of the uterine cavity. During the menstrual cycle, the endometrium is the organ in the body that shows the greatest changes under the influence of the sex hormones, oestradiol and progesterone. In the oestrogen dominated phase the endometrium proliferates until progesterone from the corpus luteum transforms the oestrogen-primed proliferative endometrium to a secretory phase endometrium. In due course this is followed by shedding of the fully transformed endometrium during the menstruation, and a new cycle will begin.

Persistent unbalanced oestrogen stimulation either due to increased endogenous production of oestrogens, or replacement therapy in which oestrogens are given alone, is associated with increased risk of developing endometrial hyperplasia and subsequently endometrial adenocarcinoma. Histologically, these pathological conditions are characterised by increased thickness of the endometrium and irregular pattern of the endometrial glandular cells.

Endometrial adenocarcinoma is a life threatening condition.

At present the endometrial status is assessed by histological and biochemical analysis of endometrial biopsies. This is time-consuming, expensive and causes discomfort for the woman. It would be highly desirable to identify biochemical markers which could be measured in body fluids reflecting the endometrial status, obviating the need for endometrial biopsies. The detection of such markers in histological samples would also however be advantageous as an additional method of recognising the histological status of such samples.

We have now discovered that certain proteins are produced in the endometrium in increased amounts associated with hyperplasia and that certain proteins are produced in increased amounts associated with adenocarcinoma. These two groups of proteins overlap somewhat. The present invention relates in a first aspect to such proteins and to their diagnostic uses.

Unless otherwise indicated, references to the proteins herein include references to modified forms of the proteins and derivatives of the proteins, including but not restricted to glycosylated, phosphorylated, acetylated, methylated or lipidated forms thereof.

Thus the invention provides a method of characterising a biological sample comprising detecting or quantitating therein one or more proteins produced by the endometrium in increased amounts in hyperplasia or in adenocarcinoma as shown by 2D gel electrophoresis comparison of cell lysates of endometrial biopsies from normal endometrium and endometrium showing hyperplasia or adenocarcinoma, excluding variations due to the menstrual cycle, or detecting or quantitating a fragment or breakdown product thereof, or a nucleic acid coding therefor, or an antibody thereto.

The invention includes a method of characterising a biological sample comprising detecting or quantitating therein one or more proteins produced by the endometrium in increased amounts in hyperplasia or in adenocarcinoma and characterised by one of the following combinations of molecular weight and pI values:

hyperplasia	
pI	MW kDa
6.7	91
6.6	90
6.9	64
6.6	67
6.3	66
6.8	46
5.7	41
5.5	35
5.3	13
6.6	101
5.8	14
7.4	51
8.2	44
9.5	48

	adenocarcinoma	
	pI	MW (kDa)
	6.3	32
	6.0	109
	6.7	91
	6.6	90
	6.9	64
	6.6	67
	6.3	66
	6.2	62
	6.2	45
	5.7	45
	5.4	33
	6.3	27
	6.5	103
	6.8	90
	6.9	78
	5.3	13
	6.2	130
	6.3	66
	6.3	73
	8.3	32
	8.1	55
	8.2	44
	6.6	111
	7.7	43
	9.5	48
	8.3	32
	7.7	39

or a fragment or breakdown product thereof, or a nucleic acid coding therefor, or an antibody thereto.

Said protein, fragment, breakdown product, antibody or nucleic acid may preferably be detected in a body fluid sample but may also be detailed in other forms of sample such as histological samples or cytological samples.

The invention includes an immunological binding partner specifically reactive with a protein as defined above with a fragment or breakdown product thereof or with a nucelic acid coding therefor.

It also includes a cell line producing a monoclonal antibody being such an immunological binding partner.

The invention includes also an assay kit for use in such an analysis method comprising an immunological binding partner as described.

This aspect of the invention has resulted from studies aiming to detect endometrial proteins with increased synthesis in endometrial adenocarcinoma as compared to the synthesis during the normal menstrual cycle; to detect endometrial proteins with increased synthesis in endometrial hyperplasia as compared to the synthesis during the normal menstrual cycle; and to detect proteins showing a cycle-related expression during the normal menstrual cycle.

In a second aspect the invention relates to the discovery of markers of the "proliferative" phase of the human endometrium. A protein marker for the "secretory" phase of the endometrium has been previously described, see US-A-4,489,166. No similar marker has been described for the proliferative phase although certain candidate proteins were described in Ref. 1.

Under influence of the sex hormones, oestradiol and progesterone, the human endometrium undergoes cyclical variation with an oestrogen-dominated phase, i.e. the proliferative phase, an ovulation phase, i.e. the interval phase, a progesterone-dominated phase, i.e. the secretory phase, and finally the endometrium is shed, i.e. the menstrual phase. The same cyclical variation of the endometrium is seen in postmenopausal women receiving sequentially combined hormone replacement therapy. The demand for endometrial status assessment has highly increased in the latest decade, not only on account of the extensive research into fertility, but also in order to

estimate endometrial response to the large number of combined oestrogens/progestogen preparations used in hormone replacement therapy. It would be highly desirable to identify biochemical markers which could be measured in body fluids reflecting the endometrial status, obviating the need for endometrial biopsies. Studies have suggested that serum placental protein 14 (PP14), which is produced in the glandular cells of the secretory phase endometrium (Ref. 3), is a reliable marker of the secretory phase endometrium. It has been shown that serum PP14 strongly correlates with the secretory activity of the endometrium in postmenopausal women receiving hormone replacement therapy (Ref. 4,5). No similar marker exists for the proliferative phase endometrium.

We have now discovered that certain proteins are produced in the endometrium in increased amounts in proliferative phase endometrium as compared to secretory phase endometrium.

According to this aspect of the invention there is now provided a method of characterising a biological sample comprising detecting or quantitating therein one or more proteins produced by the endometrium in increased amounts during the proliferative phase of the endometrium as shown in 2D gel elctrophoresis comparison of cell lysates of endometrial biopsies from normal endometrium in its proliferative and secretory phases and characterised by one of the following combinations of molecular weight and pI values:-

pI	MW(kDa)
6.9	86
5.4	34
5.6	67
5.3	23
6.8	52
8.7	47
8.2	138
6.5	124
7.7	119
7.8	119
8.1	66
7.1	59
6.8	66
7.9	48
7.7	31
6.8	29
7.2	70
8.0	119
6.7	62

or a fragment or breakdown product thereof, or a nucleic acid coding therefor or an antibody thereto.

Such a method may preferably be for detecting the phase of the endometrium.

The preferred features of the first aspect of the invention apply also to this second aspect.

This aspect of the invention includes a method of determining the proliferative/secretory phase status of the endometrium comprising the quantitative or qualitative measurement in a sample of any one or more of the proteins defined above or a breakdown product or fragment thereof. It also includes an immunological binding partner for any of the said proteins, breakdown products or fragments or a cell line producing such a binding partner.

Whilst the sequences and properties of proteins discussed above relate to human proteins, the assay procedures of the invention may be practised on samples arising from other species. Especially in this context, references to proteins herein should be understood to include proteins having a degree of homology of at least 60% with the given amino acid sequences irrespective of any modifications of said amino acids. When determining homology, modified amino acids such as phosphorylated, acetylated, amidated, methylated, glycosylated or lipidated derivatives of an amino acid should thus be considered to be the same as the amino acid without any such modification. Such peptides may be derived from similar proteins from other species, e.g. other mammals such as mouse, rabbit, guinea pig, pig, or cow or may be entirely or predominantly of synthetic origin.

The degree of homology may be advantageously be at least 65%, or at least 70%. Under certain circumstances, it is advantageous that the degree of homology is even higher such as at least 80% or at least 90%. Other DNA sequences which encode substantially the same amino acid sequence as a gene encoding a marker protein, i.e. a marker gene, may be used in the practice of the present invention. These include, but are not limited to, allelic genes and homologous genes from other species.

Nucleic acid fragments comprising a nucleotide sequence which codes for a protein described above or a peptide derived from it as well as nucleic acid fragments which hybridise with these nucleic acid fragments or a part thereof under stringent hybridisation conditions, e.g. 5 mM monovalent ions (0.1xSSC), neutral pH and 65°C are important aspects of the invention. The term "highly stringent", when used in conjunction with hybrisidation conditions, is as defined in the art, i.e. 5-10°C under the melting point T_m, cf, Sambrook et al, 1989, pages 11.45 - 11.49.

By the term "nucleic acid" is meant a polynucleotide of high molecular weight which can occur as either DNA or RNA and may be either single-stranded or double-stranded.

Once the amino acid sequences of the proteins of utility in the present invention are known, it is possible to synthesise DNA or RNA probes which may be used for:

i) direct detection of DNA and RNA expressing said proteins on a fixed or frozen tissue section using, e.g. chromogenous, chemiluminescent or immunofluorescent techniques;

ii) polymerase chain reaction (PCR) or other amplification techniques; and

iii) locating the part or all of the gene, isogene, pseudogene or other related genes either in cDNA libraries, genomic libraries or other collections of genetic material from either the host or other animals, including man.

In another aspect, the invention relates to a binding means which specifically binds to a relevant protein or peptide or nucleic acid fragment as described above. In particular, the invention relates to an antibody which specifically binds to a relevant protein or peptide or an antigen-binding fragment thereof, i.e. a polyclonal antibody, a monoclonal antibody, chimeric antibody, single chain antibody fragment, Fab and Fab' fragments, and an Fab expression library.

It is contemplated that both monoclonal and polyclonal antibodies will be useful in providing the basis for one or more assays to detect relevant peptides and proteins. Antibodies which are directed against epitopes that are specific for the proteins will be most useful as cross reaction will be minimised therewith.

Based upon the identification of relevant proteins described above, assay methods and kits may be produced according to standard methodology. Thus, the proteins may be obtained in purified form, either by extraction from tissues or by synthesis, and antibodies may be raised thereto or to characterising peptide sequences thereof. Standard assay formats employing such antibodies may be utilised according to the invention.

Preferred immunoassays are contemplated as including various types of enzyme linked immunoassays (ELISA), immunoblot techniques, and the like, known in the art. However, it is readily appreciated that utility is not limited to such assays, and useful embodiments including RIAs and other non-enzyme linked antibody binding assays or procedures. The proteins themselves or peptides derived from the protein sequences may be used in detecting auto-antibodies to such proteins.

Samples of the proteins described above have been subjected to trypsin digestion and the molecular weight of the resulting fragments has been determined by mass spectrometry. This provides a "fingerprint" of the protein which can be matched to date in established data bases available to those working in this field. This procedure has enabled us to identify certain of the proteins as being previously known in other contexts. No matches have been found for certain others, indicating that they have not previously been known.

The invention will be illustrated and explained further by the following description in which the Figures as follows:-

Figure 1: Fluorograph of a two-dimensional gel electrophoresis of [^{35}S]methionine labelled endometrial proteins separated in the first dimension by isoelectric focusing (IEF; pI 3.5-7) and in the second dimension by sodium dodecyl sulphate polyacrylamide gel electrophoresis. The locations of the spots with increased synthesis in hyperplasia are indicated.

Figure 2: Fluorograph of a two-dimensional gel electrophoresis of [^{35}S]methionine labelled endometrial proteins separated in the first dimension by non-equilibrium pH gradient gel electrophoresis (NEPHGE; pI 6.5-11) and in the second dimension by sodium dodecyl sulphate polyacrylamide gel

electrophoresis. The locations of the spots with increased synthesis in hyperplasia are indicated.

Figure 3: Fluorograph of a two-dimensional gel electrophoresis of [^{35}S]methionine labelled endometrial proteins separated in the first dimension by isoelectric focusing (IEF; pI 3.5-7) and in the second dimension by sodium dodecyl sulphate polyacrylamide gel elctrophoresis. The locations of the spots with increased synthesis in adenocarcinoma are indicated.

Figure 4: Fluorograph of a two-dimensional gel electrophoresis of [^{35}S]methionine labelled endometrial proteins separated in the first dimension by non-equilibrium pH gradient gel electrophoresis (NEPHGE; pI 6.5-11) and in the second dimension by sodium dodecyl sulphate polyacrylamide gel electrophoresis. The locations of the spots with increased synthesis in adenocarcinoma are indicated.

Figure 5: Fluorograph of a two-dimensional gel electrophoresis of [^{35}S]methionine labelled endometrial proteins separated in the first dimension by isoelectric focusing (IEF; pI 3.5-7) and in the second dimension by sodium dodecyl sulphate polyacrylamide gel elctrophoresis. The locations of the spots with increased synthesis in proliferative phase endometrium are indicated.

Figure 6: Fluorograph of a two-dimensional gel electrophoresis of [^{35}S]methionine labelled endometrial proteins separated in the first dimension by non-equilibrium pH gradient gel electrophoresis (NEPHGE; pI 6.5-11) and in the second dimension by sodium dodecyl sulphate polyacrylamide gel electrophoresis. The locations of the spots with increased synthesis in proliferative phase endometrium are indicated.

Figure 7: Tryptic digestion mass spectroscopic characteristics of I#350. The peaks marked with a star

are not protein identification specific but represents methodologically non-specific peaks.

Figure 8: Tryptic digestion mass spectroscopic characteristics of I#687. The peaks marked with a star are not protein identification specific but represents methodologically non-specific peaks.

Figure 9: Tryptic digestion mass spectroscopic characteristics of N#414. The peaks marked with a star are not protein identification specific but represents methodologically non-specific peaks.

Figure 10: Tryptic digestion mass spectroscopic characteristics of I#1035. The peaks marked with a star are not protein identification specific but represents methodologically non-specific peaks.

Figure 11:Tryptic digestion mass spectroscopic characteristics of N#26. The peaks marked with a star are not protein identification specific but represents methodologically non-specific peaks.

Figure 12:Tryptic digestion mass spectroscopic characteristics of N#31+N#32. The peaks marked with a star are not protein identification specific but represents methodologically non-specific peaks.

To identify proteins expressed at an increased level in differing endometrial conditions, endometrial samples were obtained as follows.

Normal menstrual cycle samples were obtained as described in Ref. 1. Endometrial biopsies were collected from 13 pre-menopausal, regular cycling women (35-50 years old) undergoing endometrial curettage (n=1) or hysterectomy (removal of the uterus) (n=12) for a variety of medical reasons not related to abnormality or malignancy of the endometrium. None used hormone contraception. For pathological condition samples, endometrial biopsies were collected from 16 patients (41 to 79 years old) undergoing endometrial curettage (n=9) or hysterectomy (n=7) for medical reasons related to abnormality or malignancy of the endometrium.

The samples were treated as described in Ref. 1. The proteins of the endometrial biopsies were metabolically labelled with ^{35}S-methionine for 20 hours, and total cell lysates were processed for 2D gel electrophoresis, a technique in which proteins are separated in the first dimension according to the isoelectric point and in the second dimension according to the molecular weight. It was possible to study proteins with iso-electric points ranging from 3.5 to 11 and relative molecular weights ranging from 10 to 300 kDa. After electrophoresis the gels were fixed and treated for fluorography. The fluorograms of the 2D gel electrophoresis were subjected to quantitative analysis by computer-aided analysis, by which the density of each spot was quantified, the fluorogram patterns were matched i.e. numbers were assigned to each spot and the same spot was given the same number on all the fluorograms. The density (quantity synthesis) of each spot was assessed to find proteins with increased synthesis in endometrial adenocarcinoma or hyperplasia and assessed for periodic characteristics during the normal menstrual cycle to find proteins with the menstrual cycle-related synthesis.

Some of the menstrual cycle-related proteins so identified have been identified by amino acid sequence analysis (Ref.2). Selected menstrual cycle-related proteins were excised from several 2D gels, concentrated by 1D sodium dodecylsulphate polyacrylamide gel electrophoresis, and cleaved in situ by trypsin. The tryptic fragments were extracted and separated by reverse phase high pressure liquid chromatography. Finally, the partial amino-terminal amino acid sequence of selected tryptic fragments were determined for each protein. For identification the amino acid sequences of the tryptic fragments were compared to previously reported sequences by searching in databases.

The hyperplasia and adenocarcinoma associated proteins of the present invention may be sequenced and further characterised by similar methods.

Out of a total number of approximately 1,700 spots, 14 spots were found to have increased synthesis in hyperplasia. The locations of these are shown in Figures 1 and 2. Some 27 spots had increased synthesis in adenocarcinoma. The locations of these are shown in Figures 3 and 4. The information obtained from the 2D-gel electrophoresis with respect to the isoelectric point (pI) and the molecular weight (MW) of the spots with increased synthesis in hyperplasia is given in Table 1, and the spots with increased synthesis in adenocarcinoma are listed in Table 2. Eight spots had increased expression in both hyperplasia and adenocarcinoma. Based on subjective evaluation, preferred subgroups of spots were selected with increased synthesis in hyperplasia and in adenocarcinoma, respectively. The preferred subgroup of spots with increased synthesis in hyperplasia were selected as being the spots showing the highest relative increase in expression in hyperplasia as compared to the samples obtained from women during the normal mentrual cycle and women with irregular proliferative phase endometrium. Similarly, the preferred subgroup of spots with increased synthesis in adenocarcinoma were selected as the spots showing the highest relative increase in expression in adenocarcinoma as compared to the samples obtained from women during the normal menstrual cycle and women with irregular proliferative phase endometrium. The preferred subgroup of 7 spots with increased synthesis in hyperplasia is given in Table 3, and the preferred subgroup of 12 spots with increased synthesis in adenocarcinoma is given in Table 4.

TABLE 1

Endometrial proteins with increased synthesis in hyperplasia		
Match #	pI	MW(kDa)
I#111	6.7	91
I#121	6.6	90
I#158	6.9	64
I#177	6.6	67
I#191	6.3	66
I#307	6.8	46
I#350	5.7	41
I#405	5.5	35
I#653	5.3	13
I#892	6.6	101
I#1183	5.8	14
N#126	7.4	51
N#148	8.2	44
N#414	9.5	48

Table 2

Endometrial proteins with increased synthesis in adenocarcinoma		
Match #	pI	MW(kDa)
I#16	6.3	32
I#53	6.0	109
I#111	6.7	91
I#121	6.6	90
I#158	6.9	64
I#177	6.6	67
I#191	6.3	66
I#194	6.2	62
I#337	6.2	45
I#346	5.7	45
I#436	5.4	33
I#452	6.3	27
I#542	6.5	103
I#558	6.8	90
I#627	6.9	78
I#653	5.3	13
I#788	6.2	130
I#1137	6.3	66
I#1271	6.3	73
N#15	8.3	32
N#91	8.1	55
N#148	8.2	44
N#251	6.6	111
N#354	7.7	43
N#414	9.5	48
N#549	8.3	32
N#551	7.7	39

TABLE 3

Preferred endometrial proteins with increased synthesis in hyperplasia		
Match #	pI	MW(kDa)
I#111	6.7	91
I#158	6.9	64
I#191	6.3	66
I#350	5.7	41
I#405	5.5	35
I#653	5.3	13
I#892	6.6	101

TABLE 4

Preferred endometrial proteins with increased synthesis in adenocarcinoma		
Match #	pI	MW(kDa)
I#111	6.7	91
I#158	6.9	64
I#191	6.3	66
I#194	6.2	62
I#337	6.2	45
I#346	5.7	45
I#452	6.3	27
I#627	6.9	78
I#653	5.3	13
N#91	8.1	55
N#354	7.7	43
N#551	7.7	39

Out of the total number of approximately 1,700 spots, 135 had a menstrual cycle-related expression. These 135 spots had maximal expression as follows: 61 spots in proliferative endometrium, 29 spots in interval phase endometrium, 41 in secretory phase endometrium and 4 in late secretory/menstrual phase endometrium. The information obtained from the 2D-gel electrophoresis with respect to the isoelectric point (pI) and the molecular weight (MW) of a preferred subgroup of these spots which show increased synthesis in proliferative phase endometrium are given in Table 5 and their positions are indicated in Figures 5 and 6.

TABLE 5

Endometrial proteins with menstrual cycle-related expression Maximal expression in proliferative phase endometrium		
Match #	pI	MW(kDa)
I#103	6.9	86
I#590	5.4	34
I#687	5.6	67
I#960	5.3	23
I#1035	6.8	52
N#8	8.7	47
N#21	8.2	138
N#26	6.5	124
N#31	7.7	119
N#32	7.8	119
N#64	8.1	66
N#71	7.1	59
N#74	6.8	66
N#124	7.9	48
N#192	7.7	31
N#207	6.8	29
N#265	7.2	70
N#332	8.0	119
N#342	6.7	62

Fluorographs of gels exemplifying those upon which the identifications given in Tables 1 to 5 above are based appear in Figures 1 to 6.

The proteins described above may be further characterised by partial amino acid sequence analysis as described in Ref. 2, or by the more sensitive technique of mass spectrometric peptide mapping. By way of example, we have identified the proteins for which previously given names, data-base accession numbers and amino acid sequences are given in Table 6. Mass spectroscopic characteristics of tryptic digests of further proteins are shown in Figures 7 to 13 which have not matches to any known protein. These proteins can be sequenced by known techniques and are included per se within the scope of the invention.

TABLE 6

Match #	Name ID	Amino Acid Sequence
I#191 And I#1137 SEQ ID No.1	Human heat shock 70 kD protein 1 P08107	MAKAAAIGID LGTTYSCVGV FQHGKVEIIA NDQGNRTTPS YVAFTDTERL IGDAAKNQVA LNPQNTVFDA KRLIGRKFGD PVVQSDMKHW PFQVINDGDK PKVQVSYKGE TKAFYPEEIS SMVLTKMKEI AEAYLGYPVT NAVITVPAYF NDSQRQATKD AGVIAGLNVL RIINEPTAAA IAYGLDRTGK GERNVLIFDL GGGTFDVSIL TIDDGIFEVK ATAGDTHLGG EDFDNRLVNH FVEEFKRKHK KDISQNKRAV RRLRTACERA KRTLSSSTQA SLEIDSLFEG IDFYTSITRA RFEELCSDLF RSTLEPVEKA LRDAKLDKAQ IHDLVLVGGS TRIPKVQKLL QDFFNGRDLN KSINPDEAVA YGAAVQAAIL MGDKSENVQD LLLLDVAPLS LGLETAGGVM TALIKRNSTI PTKQTQIFTT YSDNQPGVLI QVYEGERAMT KDNNLLGRFE LSGIPPAPRG VPQIEVTFDI DANGILNVTA TDKSTGKANK ITITNDKGRL SKEEIERMVQ EAEKYKAEDE VQRERVSAKN ALESYAFNMK SAVEDEGLKG KISEADKKKV LDKCQEVISW LDANTLAEKD EFEHKRKELE QVCNPIISGL YQGAGGPGPG GFGAQGPKGG SGSGPTIEEV D
I#337 SEQ ID No.2	CAMP-dependent protein kinase type I-beta regulatory chain	ASPPACPSEE DESLKGCELY VQLHGIQQVL KDCIVHLCIS KPERPMKFLR EHFEKLEKEE NRQILARQKS NSQSDSHDEE VSPTPPNPVV KARRRRGGVS AEVYTEEDAV SYVRKVIPKD YKTMTALAKA ISKNVLFAHL DDNERSDIFD AMFPVTHIAG ETVIQQGNEG DNFYVVDQGE VDVYVNGEWV TNISEGGSFG ELALIYGTPR AATVKAKTDL KLWGIDRDSY RRILMGSTLR

	P31321	KRKMYEEFLS KVSILESLEK WERLTVADRL EPVQFEDGEK IVVQGEPGDD FYIITEGTAS VLQRRSPNEE YVEVGRLGPS DYFGEIALLL NRPRAATVVA RGPLKCVKLD RPRFERVLGP CSEILKRNIQ RYNSFISLTV
I#346 And I#405 SEQ ID No.3	Vimentin P08670	STRSVSSSSY RRMFGGPGTA SRPSSSRSYV TTSTRTYSLG SALRPSTSRS LYASSPGGVY ATRSSAVRLR SSVPGVRLLQ DSVDFSLADA INTEFKNTRT NEKVELQELN DRFANYIDKV RFLEQQNKIL LAELEQLKGQ GKSRLGDLYE EEMRELRRQV DQLTNDKARV EVERDNLAED IMRLREKLQE EMLQREEAEN TLQSFRQDVD NASLARLDLE RKVESLQEEI AFLKKLHEEE IQELQAQIQE QHVQIDVDVS KPDLTAALRD VRQQYESVAA KNLQEAEEWY KSKFADLSEA ANRNNDALRQ AKQESTEYRR QVQSLTCEVD ALKGTNESLE RQMREMEENF AVEAANYQDT IGRLQDEIQN MKEEMARHLR EYQDLLNVKM ALDIEIATYR KLLEGEESRI SLPLPNFSSL NLRETNLDSL PLVDTHSKRT FLIKTVETRD GQVINETSQH HDDLE
I#452 SEQ ID No.4	Heat Shock 27 KD Protein P04792 And Prohibitin P35232 (in admixture)	MTERRVPFSL LRGPSWDPFR DWYPHSRLFD QAFGLPRLPE EWSQWLGGSS WPGYVRPLPP AAIESPAVAA PAYSRALSRQ LSSGVSEIRH TADRWRVSLD VNHFAPDELT VKTKDGVVEI TGKHEERQDE HGYISRCFTR KYTLPPGVDP TQVSSSLSPE GTLTVEAPMP KLATQSNEIT IPVTFESRAQ LGGRSCKIR MAAKVFESIG KFGLALAVAG GVVNSALYNV DAGHRAVIFD RFRGVQDIVV GEGTHFLIPW VQKPIIFDCR SRPRNVPVIT GSKDLQNVNI TLRILFRPVA SQLPRIFTSI GEDYDERVLP SITTEILKSV VARFDAGELI TQRELVSRQV SDDLTERAAT FGLILDDVSL THLTFGKEFT EAVEAKQVAQ QEAERARFVV EKAEQQKKAA IISAEGDSKA AELIANSLAT AGDGLIELRK LEAAEDIAYQ LSRSRNITYL PAGQSVLLQL PQ
I#436 And I#590 SEQ ID No.5	Tropomyosin fibroblast isoform TM3 P09494	MDAIKKKMQM LKLDKENALD RAEQAEADKK AAEDRSKQLE DELVSLQKKL KGTEDELDKY SEALKDAQEK LELAEKKATD AEADVASLNR RIQLVEEELD RAQERLATAL QKLEEAEKAA DESERGMKVI ESRAQKDEEK MEIQEIQLKE AKHIAEDADR KYEEVARKLV IIESDLERAE ERAELSEGQV RQLEEQLRIM DQTLKALMAA EDKYSQKEDR YEEEIKVLSD KLKEAETRAE FAERSVTKLE KSIDDLEEKV AHAKEENLSM HQMLDQTLLE LNNM
I#627 SEQ ID No.6	Serotrans-ferrin precursor P02787	MRLAVGALLV CAVLGLCLAV PDKTVRWCAV SEHEATKCQS FRDHMKSVIP SDGPSVACVK KASYLDCIRA IAANEADAVT LDAGLVYDAY LAPNNLKPVV AEFYGSKEDP QTFYYAVAVV KKDSGFQMNQ LRGKKSCHTG LGRSAGWNIP IGLLYCDLPE PRKPLEKAVA NFFSGSCAPC ADGTDFPQLC QLCPGCGCST LNQYFGYSGA FKCLKDGAGD VAFVKHSTIF ENLANKADRD QYELLCLDNT RKPVDEYKDC HLAQVPSHTV VARSMGGKED LIWELLNQAQ EHFGKDKSKE

		FQLFSSPHGK DLLFKDSAHG FLKVPPRMDA KMYLGYEYVT AIRNLREGTC PEAPTDECKP VKWCALSHHE RLKCDEWSVN SVGKIECVSA ETTEDCIAKI MNGEADAMSL DGGFVYIAGK CGLVPVLAEN YNKSDNCEDT PEAGYFAVAV VKKSASDLTW DNLKGKKSCH TAVGRTAGWN IPMGLLYNKI NHCRFDEFFS EGCAPGSKKD SSLCKLCMGS GLNLCEPNNK EGYYGYTGAF RCLVEKGDVA FVKHQTVPQN TGGKNPDPWA KNLNEKDYEL LCLDGTRKPV EEYANCHLAR APNHAVVTRK DKEACVHKIL RQQQHLFGSN VTDCSGNFCL FRSETKDLLF RDDTVCLAKL HDRNTYEKYL GEEYVKAVGN LRKCSTSSLL EACTFRRP
N#8 SEQ ID No.7	47 KD Heat Shock Protein Precursor P29043	MRSLLLGTLC LLAVALAAEV KKPVEAAAPG TAEKLSSKAT TLAEPSTGLA FSLYQAMAKD QAVENILVSP VVVASSLGLV SLGGKATTAS QAKAVLSAEQ LRDEEVHAGL GELLRSLSNS TARNVTWKLG SRLYGPSSVS FADDFVRSSK QHYNCEHSKI NFPDKRSALQ SINEWAAQTT DGKLPEVTKD VERTDGALLV NAMFFKPHWD EKFHHKMVDN RGFMVTRSYT VGVTMMHRTG LYNYYDDEKE KLQLVEMPLA HKLSSLIILM PHHVEPLERL EKLLTKEQLK IWMGKMQKKA VAISLPKGVV EVTHDLQKHL AGLGLTEAID KNKADLSRMS GKKDLYLASV FHATAFELDT DGNPFDQDIY GREELRSPKL FYADHPFIFL VRDTQSGSLL FIGRLVRLKG DKMRDEL
N#124 SEQ ID No.8	Ubiquinol-cytochrom C reductase complex core protein 2 precursor P22695	MKLLTRAGSF SRFYSLKVAP KVKATAAPAG APPQPQDLEF TKLPNGLVIA SLENYSPVSR IGLFIKAGSR YEDFSNLGTT HLLRLTSSLT TKGASSFKIT RGIEAVGGKL SVTATRENMA YTVECLRGDV DILMEFLLNV TTAPEFRRWE VADLQPQLKI DKAVAFQNPQ THVIENLHAA AYQNALANPL YCPDYRIGKV TSEELHYFVQ NHFTSARMAL IGLGVSHPVL KQVAEQFLNM RGGLGLSGAK ANYRGGEIRE QNGDSLVHAA FVAESAVAGS AEANAFSVLQ HVLGAGPHVK RGSNTTSHLH QAVAKATQQP FDVSAFNASY SDSGLFGIYT ISQATAAGDV IKAAYNQVKR IAQGNLSNTD VQAAKNKLKA GYLMSVESSE CFLEEVGSQA LVAGSYMPPS TVLQQIDSVA NADIINAAKK FVSGQKSMAA SGNLGHTPFV DEL
N#126 SEQ ID No.9	Alpha Enolase P06733	SILKIHAREI FDSRGNPTVE VDLFTSKGLF RAAVPSGAST GIYEALELRD NDKTRYMGKG VSKAVEHINK TIAPALVSKK LNVTEQEKID KLMIEMDGTE NKSKFGANAI LGVSLAVCKA GAVEKGVPLY RHIADLAGNS EVILPVPAFN VINGGSHAGN KLAMQEFMIL PVGAANFREA MRIGAEVYHN LKNVIKEKYG KDATNVGDEG GFAPNILENK EGLELLKTAI GKAGYTDKVV IGMDVAASEF FRSGKYDLDF KSPDDPSRYI SPDQLADLYK SFIKDYPVVS IEDPFDQDDW GAWQKFTASA GIQVVGDDLT VTNPKRIAKA VNEKSCNCLL LKVNQIGSVT ESLQACKLAQ ANGWGVMVSH RSGETEDTFI ADLVVGLCTG QIKTGAPCRS ERLAKYNQLL RIEEELGSKA KFAGRNFRNP LAK

N#148 SEQ ID No.10	Phospho-glycerate kinase 1 P00558	SLSNKLTLDK LDVKGKRVVM RVDFNVPMKNNQITNNQRIK AAVPSIKFCL DNGAKSVVLM SHLGRPDGVP MPDKYSLEPV AVELKSLLGK DVLFLKDCVG PEVEKACANP AAGSVILLEN LRFHVEEEGK GKDASGNKVK AEPAKIEAFR ASLSKLGDVY VNDAFGTAHR AHSSMVGVNL PQKAGGFLMK KELNYFAKAL ESPERPFLAI LGGAKVADKI QLINNMLDKV NEMIIGGGMA FTFLKVLNNM EIGTSLFDEE GAKIVKDLMS KAEKNGVKIT LPVDFVTADK FDENAKTGQA TVASGIPAGW MGLDCGPESS KKYAEAVTRA KQIVWNGPVG VFEWEAFARG TKALMDEVVK ATSRGCITII GGGDTATCCA KWNTEDKVSH VSTGGGASLE LLEGKVLPGV DALSNIL
N#207 SEQ ID No.11	Triose-phosphat isomerase ISHUT S29743	MAPSRKFFVG GNWKMNGRKQ SLGELIGTLN AAKVPADTEV VCAPPTAYID FARQKLDPKI AVAAQNCYKV TNGAFTGEIS PGMIKDCGAT WVVLGHSERR HVFGESDELI GQKVAHALAE GLGVIACIGE KLDEREAGIT EKVVFEQTKV IADNVKDWSK VVLAYEPVWA IGTGKTATPQ QAQEVHEKLR GWLKSNVSDA VAQSTRIIYG GSVTGATCKE LASQPDVDGF LVGGASLKPE FVDIINAKQ
N#332 SEQ ID No.12	Hypo-thetical Protein KIAA0083 P51530	PVPLSFLSTV CDPRVQDGAA ERTGAADGEE FLGGGGLPAE LFQKKVVASF PRTVLSTGMD NRYLVLAVNT VQNKEGNCEK RLVITASQSL ENKELCILRN DWCSVPVEPG DIIHLEGDCT SDTWIIDKDF GYLILYPDML ISGTSIASSI RCMRRAVLSE TFRSSDPATR QMLIGTVLHE VFQKAINNSF APEKLQELAF QTIQEIRHLK EMYRLNLSQD EIKQEVEDYL PSFCKWAGDF MHKNTSTDFP QMQLSLPSDN SKDNSTCNIE VVKPMDIEES IWSPRFGLKG KIDVTVGVKI HRGYKTKYKI MPLELKTGKE SNSIEHRSQV VLYTLLSQER RADPEAGLLL YLKTGQMYPV PANHLDKREL LKLRNQMAFS LFHRISKSAT RQKTQLASLP QIIEEEKTCK YCSQIGNCAL YSRAVEQQMD CSSVPIVMLP KIEEETQHLK QTHLEYFSLW CLMLTLESQS KDNKKNHQNI WLMPASEMEK SGSCIGNLIR MEHVKIVCDG QYLHNFQCKH GAIPVTNLMA GDRVIVSGEE RSLFALSRGY VKEINMTTVT CLLDRNLSVL PESTLFRLDQ EEKNCDIDTP LGNLSKLMEN TFVSKKLRDL IIDFREPQFI SYLSSVLPHD AKDTVACILK GLNKPQRQAM KKVLLSKDYT LIVGMPGTGK TTTICTLVRI LYACGFSVLL TSYTHSAVDN ILLKLAKFKI GFLRLGQIQK VHPAIQQFTE QEICRSKSIK SLALLEELYN SQLIVATTCM GINHPIFSRK IFDFCIVDEA SQISQPICLG PLFFSRRFVL VGDHQQLPPL VLNREARALG MSESLFKRLE QNKSAVVQLT VQYRMNSKIM SLSNKLTYEG KLECGSDKVA NAVINLRHFK DVKLELEFYA DYSDNPWLMG VFEPNNPVCF LNTDKVPAPE QVEKGGVSNV TEAKLIVFLT SIFVKAGCSP SDIGIIAPYR QQLKIINDLL ARSIGMVEVN TVDKYQGRDK SIVLVSFVRS NKDGTVGELL KDWRRLNVAI TRAKHKLILL GCVPSLNCYP PLEKLLNHLN

		SEKLIIDLPS REHESLCHIL GDFQRE
N#342 SEQ ID No.13	Catalase P04040	MADSRDPASD QMQHWKEQRA AQKADVLTTG AGNPVGDKLN VITVGPRGPL LVQDVVFTDE MAHFDRERIP ERVVHAKGAG AFGYFEVTHD ITKYSKAKVF EHIGKKTPIA VRFSTVAGES GSADTVRDPR GFAVKFYTED GNWDLVGNNT PIFFIRDPIL FPSFIHSQKR NPQTHLKDPD MVWDFWSLRP ESLHQVSFLF SDRGIPDGHR HMNGYGSHTF KLVNANGEAV YCKFHYKTDQ GIKNLSVEDA ARLSQEDPDY GIRDLFNAIA TGKYPSWTFY IQVMTFNQAE TFPFNPFDLT KVWPHKDYPL IPVGKLVLNR NPVNYFAEVE QIAFDPSNMP PGIEASPDKM LQGRLFAYPD THRHRLGPNY LHIPVNCPYR ARVANYQRDG PMCMQDNQGG APNYYPNSFG APEQQPSALE HSIQYSGEVR RFNTANDDNV TQVRAFYVNV LNEEQRKRLC ENIAGHLKDA QIFIQKKAVK NFTEVHPDYG SHIQALLDKY NAEKPKNAIH TFVQSGSHLA AREKANL
N#551 SEQ ID No.14	Hetero- geneous nuclear ribonucleo- proteins A2/B1 P22626	MEKTLETVPL ERKKREKEQF RKLFIGGLSF ETTEESLRNY YEQWGKLTDC VVMRDPASKR SRGFGFVTFS SMAEVDAAMA ARPHSIDGRV VEPKRAVARE ESGKPGAHVT VKKLFVGGIK EDTEEHHLRD YFEEYGKIDT IEIITDRQSG KKRGFGFVTF DDHDPVDKIV LQKYHTINGH NAEVRKALSR QEMQEVQSSR SGRGGNFGFG DSRGGGGNFG PGPGSNFRGG SDGYGSGRGF GDGYNGYGGG PGGGNFGGSP GYGGGRGGYG GGGPGYGNQG GGYGGGYDNY GGGNYGSGNY NDFGNYNQQP SNYGPMKSGN FGGSRNMGGP YGGGNYGPGG SGGSGGYGGR SRY
I#960 (Prolifer ative phase marker) SEQ ID No.15	Steroid membrane binding protein X99714	MAAEDVAATG ADPSELEGGG LLHEIFTSPL NLLLLGLCIF LLYKIVRGDQ PAASDSDDDE PPPLPRLKRR DFTPAELRRF DGVQDPRILM AINGKVFDVT KGRKFYGPEG PYGVFAGRDA SRGLATFCLD KEALKDEYDD LSDLTPAQQE TLNDWDSQFT FKYHHVGKLL KEGEEPTVYS DEEEPKDESA RKND
I#177 (Hyperpla sia & Cancer Marker) SEQ ID No.16	Heat shock cognate 71 KD protein P11142	MSKGPAVGID LGTTYSCVGV FQHGKVEIIA NDQGNRTTPS YVAFTDTERL IGDAAKNQVA MNPTNTVFDA KRLIGRRFDD AVVQSDMKHW PFMVVNDAGR PKVQVEYKGE TKSFYPEEVS SMVLTKMKEI AEAYLGKTVT NAVVTVPAYF NDSQRQATKD AGTIAGLNVL RIINEPTAAA IAYGLDKKVG AERNVLIFDL GGGTFDVSIL TIEDGIFEVK STAGDTHLGG EDFDNRMVNH FIAEFKRKHK KDISENKRAV RRLRTACERA KRTLSSSTQA SIEIDSLYEG IDFYTSITRA RFEELNADLF RGTLDPVEKA LRDAKLDKSQ IHDIVLVGGS TRIPKIQKLL QDFFNGKELN KSINPDEAVA YGAAVQAAIL SGDKSENVQD LLLLDVTPLS LGIETAGGVM TVLIKRNTTI PTKQTQTFTT YSDNQPGVLI QVYEGERAMT KDNNLLGKFE LTGIPPAPRG VPQIEVTFDI DANGILNVSA VDKSTGKENK ITITNDKGRL SKEDIERMVQ EAEKYKAEDE KQRDKVSSKN SLESYAFNMK ATVEDEKLQG KINDEDKQKI LDKCNEIINW LDKNQTAEKE EFEHQQKELE KVCNPIITKL YQSAGGMPGG MPGGFPGGGA PPSGGASSGP TIEEVD

ID: Accession Identification in protein or nucleotide databases (e.g. SwissProt, Protein Identification Resource (PIR) or EMBL)

The proteins of interest may be isolated from endometrial tissue or other protein sources by 2D gel electrophoresis or by using chromatographic techniques. Poly- or monoclonal antibodies towards the protein of interest can be raised, and immunoassays can be established based on such antibodies. Synthetic peptides being fragments characteristic of such proteins may be used for the same purposes. Assays may be based on more than one such protein for measurement at one time.

Ref.1 : Byrjalsen et al. Hum Reprod 1995;10:13-18.
Ref.2 : Byrjalsen et al., Hum Reprod 1995;10:2760-2766.
Ref.3 : Julkunen et al., Endocrinology 1986;118:1782-1786.
Ref.4 : Byrjalsen et al., Obstet Gynecol 1992;79:523-528.
Ref.5 : Byrjalsen et al., Hum Reprod 1992;7:1042-1047.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:

(A) NAME: Center for Clinical and Basic Research

(B) STREET: Ballerup Byvej 222,
(C) CITY: Ballerup
(E) COUNTRY: Denmark
(F) POSTAL CODE (ZIP): DK-2750

(ii) TITLE OF INVENTION: Biochemical Markers for the Human Endometrium

(iii) NUMBER OF SEQUENCES: 16

(iv) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

(vi) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: GB 9618600.2
(B) FILING DATE: 06-SEP-1996

(vi) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: GB 9707132.8
(B) FILING DATE: 08-APR-1997

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 641 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

```
Met Ala Lys Ala Ala Ala Ile Gly Ile Asp Leu Gly Thr Thr Tyr Ser
1               5                  10                  15

Cys Val Gly Val Phe Gln His Gly Lys Val Glu Ile Ile Ala Asn Asp
            20                  25                  30

Gln Gly Asn Arg Thr Thr Pro Ser Tyr Val Ala Phe Thr Asp Thr Glu
        35                  40                  45
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Arg Leu Ile Gly Asp Ala Ala Lys Asn Gln Val Ala Leu Asn Pro Gln
50 55 60

Asn Thr Val Phe Asp Ala Lys Arg Leu Ile Gly Arg Lys Phe Gly Asp
65 70 75 80

Pro Val Val Gln Ser Asp Met Lys His Trp Pro Phe Gln Val Ile Asn
85 90 95

Asp Gly Asp Lys Pro Lys Val Gln Val Ser Tyr Lys Gly Glu Thr Lys
100 105 110

Ala Phe Tyr Pro Glu Glu Ile Ser Ser Met Val Leu Thr Lys Met Lys
115 120 125

Glu Ile Ala Glu Ala Tyr Leu Gly Tyr Pro Val Thr Asn Ala Val Ile
130 135 140

Thr Val Pro Ala Tyr Phe Asn Asp Ser Gln Arg Gln Ala Thr Lys Asp
145 150 155 160

Ala Gly Val Ile Ala Gly Leu Asn Val Leu Arg Ile Ile Asn Glu Pro
165 170 175

Thr Ala Ala Ala Ile Ala Tyr Gly Leu Asp Arg Thr Gly Lys Gly Glu
180 185 190

Arg Asn Val Leu Ile Phe Asp Leu Gly Gly Gly Thr Phe Asp Val Ser
195 200 205

Ile Leu Thr Ile Asp Asp Gly Ile Phe Glu Val Lys Ala Thr Ala Gly
210 215 220

Asp Thr His Leu Gly Gly Glu Asp Phe Asp Asn Arg Leu Val Asn His
225 230 235 240

Phe Val Glu Glu Phe Lys Arg Lys His Lys Lys Asp Ile Ser Gln Asn
245 250 255

Lys Arg Ala Val Arg Arg Leu Arg Thr Ala Cys Glu Arg Ala Lys Arg
260 265 270

Thr Leu Ser Ser Ser Thr Gln Ala Ser Leu Glu Ile Asp Ser Leu Phe
275 280 285

Glu Gly Ile Asp Phe Tyr Thr Ser Ile Thr Arg Ala Arg Phe Glu Glu
290 295 300

Leu Cys Ser Asp Leu Phe Arg Ser Thr Leu Glu Pro Val Glu Lys Ala
305 310 315 320

Leu Arg Asp Ala Lys Leu Asp Lys Ala Gln Ile His Asp Leu Val Leu
325 330 335

Val Gly Gly Ser Thr Arg Ile Pro Lys Val Gln Lys Leu Leu Gln Asp
340 345 350

Phe Phe Asn Gly Arg Asp Leu Asn Lys Ser Ile Asn Pro Asp Glu Ala
355 360 365

Val Ala Tyr Gly Ala Ala Val Gln Ala Ala Ile Leu Met Gly Asp Lys
370 375 380

Ser Glu Asn Val Gln Asp Leu Leu Leu Leu Asp Val Ala Pro Leu Ser
385 390 395 400

Leu Gly Leu Glu Thr Ala Gly Gly Val Met Thr Ala Leu Ile Lys Arg
405 410 415

Asn Ser Thr Ile Pro Thr Lys Gln Thr Gln Ile Phe Thr Thr Tyr Ser
420 425 430

Asp Asn Gln Pro Gly Val Leu Ile Gln Val Tyr Glu Gly Glu Arg Ala
435 440 445

Met Thr Lys Asp Asn Asn Leu Leu Gly Arg Phe Glu Leu Ser Gly Ile
450 455 460

Pro Pro Ala Pro Arg Gly Val Pro Gln Ile Glu Val Thr Phe Asp Ile
465 470 475 480

Asp Ala Asn Gly Ile Leu Asn Val Thr Ala Thr Asp Lys Ser Thr Gly
485 490 495

Lys Ala Asn Lys Ile Thr Ile Thr Asn Asp Lys Gly Arg Leu Ser Lys
500 505 510

Glu Glu Ile Glu Arg Met Val Gln Glu Ala Glu Lys Tyr Lys Ala Glu
515 520 525

Asp Glu Val Gln Arg Glu Arg Val Ser Ala Lys Asn Ala Leu Glu Ser
530 535 540

Tyr Ala Phe Asn Met Lys Ser Ala Val Glu Asp Glu Gly Leu Lys Gly
545 550 555 560

Lys Ile Ser Glu Ala Asp Lys Lys Lys Val Leu Asp Lys Cys Gln Glu
565 570 575

Val Ile Ser Trp Leu Asp Ala Asn Thr Leu Ala Glu Lys Asp Glu Phe
580 585 590

Glu His Lys Arg Lys Glu Leu Glu Gln Val Cys Asn Pro Ile Ile Ser
595 600 605

Gly Leu Tyr Gln Gly Ala Gly Gly Pro Gly Pro Gly Gly Phe Gly Ala
610 615 620

Gln Gly Pro Lys Gly Gly Ser Gly Ser Gly Pro Thr Ile Glu Glu Val
625 630 635 640

Asp

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 380 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Ala Ser Pro Pro Ala Cys Pro Ser Glu Glu Asp Glu Ser Leu Lys Gly
1 5 10 15

Cys Glu Leu Tyr Val Gln Leu His Gly Ile Gln Gln Val Leu Lys Asp
20 25 30

Cys Ile Val His Leu Cys Ile Ser Lys Pro Glu Arg Pro Met Lys Phe
35 40 45

Leu Arg Glu His Phe Glu Lys Leu Glu Lys Glu Glu Asn Arg Gln Ile
50 55 60

Leu Ala Arg Gln Lys Ser Asn Ser Gln Ser Asp Ser His Asp Glu Glu
65 70 75 80

Val Ser Pro Thr Pro Pro Asn Pro Val Val Lys Ala Arg Arg Arg Arg
85 90 95

Gly Gly Val Ser Ala Glu Val Tyr Thr Glu Glu Asp Ala Val Ser Tyr
100 105 110

Val Arg Lys Val Ile Pro Lys Asp Tyr Lys Thr Met Thr Ala Leu Ala
115 120 125

Lys Ala Ile Ser Lys Asn Val Leu Phe Ala His Leu Asp Asp Asn Glu
130 135 140

Arg Ser Asp Ile Phe Asp Ala Met Phe Pro Val Thr His Ile Ala Gly
145 150 155 160

Glu Thr Val Ile Gln Gln Gly Asn Glu Gly Asp Asn Phe Tyr Val Val
165 170 175

Asp Gln Gly Glu Val Asp Val Tyr Val Asn Gly Glu Trp Val Thr Asn
180 185 190

Ile Ser Glu Gly Gly Ser Phe Gly Glu Leu Ala Leu Ile Tyr Gly Thr
195 200 205

Pro Arg Ala Ala Thr Val Lys Ala Lys Thr Asp Leu Lys Leu Trp Gly
210 215 220

Ile Asp Arg Asp Ser Tyr Arg Arg Ile Leu Met Gly Ser Thr Leu Arg
225 230 235 240

Lys Arg Lys Met Tyr Glu Glu Phe Leu Ser Lys Val Ser Ile Leu Glu
245 250 255

Ser Leu Glu Lys Trp Glu Arg Leu Thr Val Ala Asp Arg Leu Glu Pro
260 265 270

Val Gln Phe Glu Asp Gly Glu Lys Ile Val Val Gln Gly Glu Pro Gly
275 280 285

Asp Asp Phe Tyr Ile Ile Thr Glu Gly Thr Ala Ser Val Leu Gln Arg
290 295 300

Arg Ser Pro Asn Glu Glu Tyr Val Glu Val Gly Arg Leu Gly Pro Ser
305 310 315 320

Asp Tyr Phe Gly Glu Ile Ala Leu Leu Leu Asn Arg Pro Arg Ala Ala
325 330 335

Thr Val Val Ala Arg Gly Pro Leu Lys Cys Val Lys Leu Asp Arg Pro
340 345 350

Arg Phe Glu Arg Val Leu Gly Pro Cys Ser Glu Ile Leu Lys Arg Asn
355 360 365

Ile Gln Arg Tyr Asn Ser Phe Ile Ser Leu Thr Val
370 375 380

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 465 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

Ser Thr Arg Ser Val Ser Ser Ser Ser Tyr Arg Arg Met Phe Gly Gly
1 5 10 15

Pro Gly Thr Ala Ser Arg Pro Ser Ser Ser Arg Ser Tyr Val Thr Thr
20 25 30

Ser Thr Arg Thr Tyr Ser Leu Gly Ser Ala Leu Arg Pro Ser Thr Ser
35 40 45

Arg Ser Leu Tyr Ala Ser Ser Pro Gly Gly Val Tyr Ala Thr Arg Ser
50 55 60

Ser Ala Val Arg Leu Arg Ser Ser Val Pro Gly Val Arg Leu Leu Gln
65 70 75 80

Asp Ser Val Asp Phe Ser Leu Ala Asp Ala Ile Asn Thr Glu Phe Lys
85 90 95

Asn Thr Arg Thr Asn Glu Lys Val Glu Leu Gln Glu Leu Asn Asp Arg
100 105 110

Phe Ala Asn Tyr Ile Asp Lys Val Arg Phe Leu Glu Gln Gln Asn Lys
115 120 125

Ile Leu Leu Ala Glu Leu Glu Gln Leu Lys Gly Gln Gly Lys Ser Arg
130 135 140

Leu Gly Asp Leu Tyr Glu Glu Glu Met Arg Glu Leu Arg Arg Gln Val
145 150 155 160

Asp Gln Leu Thr Asn Asp Lys Ala Arg Val Glu Val Glu Arg Asp Asn
165 170 175

Leu Ala Glu Asp Ile Met Arg Leu Arg Glu Lys Leu Gln Glu Glu Met
180 185 190

Leu Gln Arg Glu Glu Ala Glu Asn Thr Leu Gln Ser Phe Arg Gln Asp
195 200 205

Val Asp Asn Ala Ser Leu Ala Arg Leu Asp Leu Glu Arg Lys Val Glu
210 215 220

Ser Leu Gln Glu Glu Ile Ala Phe Leu Lys Lys Leu His Glu Glu Glu
225 230 235 240

Ile Gln Glu Leu Gln Ala Gln Ile Gln Glu Gln His Val Gln Ile Asp
245 250 255

Val Asp Val Ser Lys Pro Asp Leu Thr Ala Ala Leu Arg Asp Val Arg
260 265 270

Gln Gln Tyr Glu Ser Val Ala Ala Lys Asn Leu Gln Glu Ala Glu Glu
275 280 285

Trp Tyr Lys Ser Lys Phe Ala Asp Leu Ser Glu Ala Ala Asn Arg Asn
290 295 300

Asn Asp Ala Leu Arg Gln Ala Lys Gln Glu Ser Thr Glu Tyr Arg Arg
305 310 315 320

Gln Val Gln Ser Leu Thr Cys Glu Val Asp Ala Leu Lys Gly Thr Asn
325 330 335

Glu Ser Leu Glu Arg Gln Met Arg Glu Met Glu Glu Asn Phe Ala Val
340 345 350

Glu Ala Ala Asn Tyr Gln Asp Thr Ile Gly Arg Leu Gln Asp Glu Ile
355 360 365

Gln Asn Met Lys Glu Glu Met Ala Arg His Leu Arg Glu Tyr Gln Asp
370 375 380

Leu Leu Asn Val Lys Met Ala Leu Asp Ile Glu Ile Ala Thr Tyr Arg
385 390 395 400

Lys Leu Leu Glu Gly Glu Glu Ser Arg Ile Ser Leu Pro Leu Pro Asn
405 410 415

Phe Ser Ser Leu Asn Leu Arg Glu Thr Asn Leu Asp Ser Leu Pro Leu
420 425 430

Val Asp Thr His Ser Lys Arg Thr Phe Leu Ile Lys Thr Val Glu Thr
435 440 445

Arg Asp Gly Gln Val Ile Asn Glu Thr Ser Gln His His Asp Asp Leu
450 455 460

Glu
465

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 471 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Met Thr Glu Arg Arg Val Pro Phe Ser Leu Leu Arg Gly Pro Ser Trp
1 5 10 15

Asp Pro Phe Arg Asp Trp Tyr Pro His Ser Arg Leu Phe Asp Gln Ala
20 25 30

Phe Gly Leu Pro Arg Leu Pro Glu Glu Trp Ser Gln Trp Leu Gly Gly
35 40 45

Ser Ser Trp Pro Gly Tyr Val Arg Pro Leu Pro Pro Ala Ala Ile Glu
50 55 60

Ser Pro Ala Val Ala Ala Pro Ala Tyr Ser Arg Ala Leu Ser Arg Gln
65 70 75 80

Leu Ser Ser Gly Val Ser Glu Ile Arg His Thr Ala Asp Arg Trp Arg
85 90 95

Val Ser Leu Asp Val Asn His Phe Ala Pro Asp Glu Leu Thr Val Lys
100 105 110

Thr Lys Asp Gly Val Val Glu Ile Thr Gly Lys His Glu Glu Arg Gln
115 120 125

Asp Glu His Gly Tyr Ile Ser Arg Cys Phe Thr Arg Lys Tyr Thr Leu
130 135 140

Pro Pro Gly Val Asp Pro Thr Gln Val Ser Ser Ser Leu Ser Pro Glu
145 150 155 160

Gly Thr Leu Thr Val Glu Ala Pro Met Pro Lys Leu Ala Thr Gln Ser
165 170 175

Asn Glu Ile Thr Ile Pro Val Thr Phe Glu Ser Arg Ala Gln Leu Gly
180 185 190

Gly Arg Ser Cys Lys Ile Arg Met Ala Ala Lys Val Phe Glu Ser Ile
195 200 205

Gly Lys Phe Gly Leu Ala Leu Ala Val Ala Gly Gly Val Val Asn Ser
210 215 220

```
Ala Leu Tyr Asn Val Asp Ala Gly His Arg Ala Val Ile Phe Asp Arg
225                 230                 235                 240

Phe Arg Gly Val Gln Asp Ile Val Val Gly Glu Gly Thr His Phe Leu
                245                 250                 255

Ile Pro Trp Val Gln Lys Pro Ile Ile Phe Asp Cys Arg Ser Arg Pro
            260                 265                 270

Arg Asn Val Pro Val Ile Thr Gly Ser Lys Asp Leu Gln Asn Val Asn
        275                 280                 285

Ile Thr Leu Arg Ile Leu Phe Arg Pro Val Ala Ser Gln Leu Pro Arg
    290                 295                 300

Ile Phe Thr Ser Ile Gly Glu Asp Tyr Asp Glu Arg Val Leu Pro Ser
305                 310                 315                 320

Ile Thr Thr Glu Ile Leu Lys Ser Val Val Ala Arg Phe Asp Ala Gly
                325                 330                 335

Glu Leu Ile Thr Gln Arg Glu Leu Val Ser Arg Gln Val Ser Asp Asp
            340                 345                 350

Leu Thr Glu Arg Ala Ala Thr Phe Gly Leu Ile Leu Asp Asp Val Ser
        355                 360                 365

Leu Thr His Leu Thr Phe Gly Lys Glu Phe Thr Glu Ala Val Glu Ala
    370                 375                 380

Lys Gln Val Ala Gln Gln Glu Ala Glu Arg Ala Arg Phe Val Val Glu
385                 390                 395                 400

Lys Ala Glu Gln Gln Lys Lys Ala Ala Ile Ile Ser Ala Glu Gly Asp
                405                 410                 415

Ser Lys Ala Ala Glu Leu Ile Ala Asn Ser Leu Ala Thr Ala Gly Asp
            420                 425                 430

Gly Leu Ile Glu Leu Arg Lys Leu Glu Ala Ala Glu Asp Ile Ala Tyr
        435                 440                 445

Gln Leu Ser Arg Ser Arg Asn Ile Thr Tyr Leu Pro Ala Gly Gln Ser
    450                 455                 460

Val Leu Leu Gln Leu Pro Gln
465                 470
```

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 284 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

```
Met Asp Ala Ile Lys Lys Lys Met Gln Met Leu Lys Leu Asp Lys Glu
1               5                  10                  15

Asn Ala Leu Asp Arg Ala Glu Gln Ala Glu Ala Asp Lys Lys Ala Ala
            20                  25                  30

Glu Asp Arg Ser Lys Gln Leu Glu Asp Glu Leu Val Ser Leu Gln Lys
        35                  40                  45

Lys Leu Lys Gly Thr Glu Asp Glu Leu Asp Lys Tyr Ser Glu Ala Leu
    50                  55                  60

Lys Asp Ala Gln Glu Lys Leu Glu Leu Ala Glu Lys Lys Ala Thr Asp
65                  70                  75                  80

Ala Glu Ala Asp Val Ala Ser Leu Asn Arg Arg Ile Gln Leu Val Glu
                85                  90                  95

Glu Glu Leu Asp Arg Ala Gln Glu Arg Leu Ala Thr Ala Leu Gln Lys
            100                 105                 110

Leu Glu Glu Ala Glu Lys Ala Ala Asp Glu Ser Glu Arg Gly Met Lys
        115                 120                 125

Val Ile Glu Ser Arg Ala Gln Lys Asp Glu Glu Lys Met Glu Ile Gln
    130                 135                 140

Glu Ile Gln Leu Lys Glu Ala Lys His Ile Ala Glu Asp Ala Asp Arg
145                 150                 155                 160

Lys Tyr Glu Glu Val Ala Arg Lys Leu Val Ile Ile Glu Ser Asp Leu
                165                 170                 175

Glu Arg Ala Glu Glu Arg Ala Glu Leu Ser Glu Gly Gln Val Arg Gln
            180                 185                 190

Leu Glu Glu Gln Leu Arg Ile Met Asp Gln Thr Leu Lys Ala Leu Met
        195                 200                 205

Ala Ala Glu Asp Lys Tyr Ser Gln Lys Glu Asp Arg Tyr Glu Glu Glu
    210                 215                 220

Ile Lys Val Leu Ser Asp Lys Leu Lys Glu Ala Glu Thr Arg Ala Glu
225                 230                 235                 240

Phe Ala Glu Arg Ser Val Thr Lys Leu Glu Lys Ser Ile Asp Asp Leu
                245                 250                 255

Glu Glu Lys Val Ala His Ala Lys Glu Glu Asn Leu Ser Met His Gln
            260                 265                 270

Met Leu Asp Gln Thr Leu Leu Glu Leu Asn Asn Met
        275                 280
```

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 698 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Met Arg Leu Ala Val Gly Ala Leu Leu Val Cys Ala Val Leu Gly Leu
1 5 10 15

Cys Leu Ala Val Pro Asp Lys Thr Val Arg Trp Cys Ala Val Ser Glu
20 25 30

His Glu Ala Thr Lys Cys Gln Ser Phe Arg Asp His Met Lys Ser Val
35 40 45

Ile Pro Ser Asp Gly Pro Ser Val Ala Cys Val Lys Lys Ala Ser Tyr
50 55 60

Leu Asp Cys Ile Arg Ala Ile Ala Ala Asn Glu Ala Asp Ala Val Thr
65 70 75 80

Leu Asp Ala Gly Leu Val Tyr Asp Ala Tyr Leu Ala Pro Asn Asn Leu
85 90 95

Lys Pro Val Val Ala Glu Phe Tyr Gly Ser Lys Glu Asp Pro Gln Thr
100 105 110

Phe Tyr Tyr Ala Val Ala Val Val Lys Lys Asp Ser Gly Phe Gln Met
115 120 125

Asn Gln Leu Arg Gly Lys Lys Ser Cys His Thr Gly Leu Gly Arg Ser
130 135 140

Ala Gly Trp Asn Ile Pro Ile Gly Leu Leu Tyr Cys Asp Leu Pro Glu
145 150 155 160

Pro Arg Lys Pro Leu Glu Lys Ala Val Ala Asn Phe Phe Ser Gly Ser
165 170 175

Cys Ala Pro Cys Ala Asp Gly Thr Asp Phe Pro Gln Leu Cys Gln Leu
180 185 190

Cys Pro Gly Cys Gly Cys Ser Thr Leu Asn Gln Tyr Phe Gly Tyr Ser
195 200 205

Gly Ala Phe Lys Cys Leu Lys Asp Gly Ala Gly Asp Val Ala Phe Val
210 215 220

Lys His Ser Thr Ile Phe Glu Asn Leu Ala Asn Lys Ala Asp Arg Asp
225 230 235 240

Gln Tyr Glu Leu Leu Cys Leu Asp Asn Thr Arg Lys Pro Val Asp Glu
245 250 255

Tyr Lys Asp Cys His Leu Ala Gln Val Pro Ser His Thr Val Val Ala
260 265 270

Arg Ser Met Gly Gly Lys Glu Asp Leu Ile Trp Glu Leu Leu Asn Gln
275 280 285

Ala Gln Glu His Phe Gly Lys Asp Lys Ser Lys Glu Phe Gln Leu Phe
290 295 300

Ser Ser Pro His Gly Lys Asp Leu Leu Phe Lys Asp Ser Ala His Gly
305 310 315 320

Phe Leu Lys Val Pro Pro Arg Met Asp Ala Lys Met Tyr Leu Gly Tyr
325 330 335

Glu Tyr Val Thr Ala Ile Arg Asn Leu Arg Glu Gly Thr Cys Pro Glu
340 345 350

Ala Pro Thr Asp Glu Cys Lys Pro Val Lys Trp Cys Ala Leu Ser His
355 360 365

His Glu Arg Leu Lys Cys Asp Glu Trp Ser Val Asn Ser Val Gly Lys
370 375 380

Ile Glu Cys Val Ser Ala Glu Thr Thr Glu Asp Cys Ile Ala Lys Ile
385 390 395 400

Met Asn Gly Glu Ala Asp Ala Met Ser Leu Asp Gly Gly Phe Val Tyr
405 410 415

Ile Ala Gly Lys Cys Gly Leu Val Pro Val Leu Ala Glu Asn Tyr Asn
420 425 430

Lys Ser Asp Asn Cys Glu Asp Thr Pro Glu Ala Gly Tyr Phe Ala Val
435 440 445

Ala Val Val Lys Lys Ser Ala Ser Asp Leu Thr Trp Asp Asn Leu Lys
450 455 460

Gly Lys Lys Ser Cys His Thr Ala Val Gly Arg Thr Ala Gly Trp Asn
465 470 475 480

Ile Pro Met Gly Leu Leu Tyr Asn Lys Ile Asn His Cys Arg Phe Asp
485 490 495

Glu Phe Phe Ser Glu Gly Cys Ala Pro Gly Ser Lys Lys Asp Ser Ser
500 505 510

Leu Cys Lys Leu Cys Met Gly Ser Gly Leu Asn Leu Cys Glu Pro Asn
515 520 525

Asn Lys Glu Gly Tyr Tyr Gly Tyr Thr Gly Ala Phe Arg Cys Leu Val
530 535 540

Glu Lys Gly Asp Val Ala Phe Val Lys His Gln Thr Val Pro Gln Asn
545 550 555 560

Thr Gly Gly Lys Asn Pro Asp Pro Trp Ala Lys Asn Leu Asn Glu Lys
565 570 575

Asp Tyr Glu Leu Leu Cys Leu Asp Gly Thr Arg Lys Pro Val Glu Glu
580 585 590

```
Tyr Ala Asn Cys His Leu Ala Arg Ala Pro Asn His Ala Val Val Thr
        595                 600                 605

Arg Lys Asp Lys Glu Ala Cys Val His Lys Ile Leu Arg Gln Gln Gln
    610                 615                 620

His Leu Phe Gly Ser Asn Val Thr Asp Cys Ser Gly Asn Phe Cys Leu
625                 630                 635                 640

Phe Arg Ser Glu Thr Lys Asp Leu Leu Phe Arg Asp Asp Thr Val Cys
                645                 650                 655

Leu Ala Lys Leu His Asp Arg Asn Thr Tyr Glu Lys Tyr Leu Gly Glu
            660                 665                 670

Glu Tyr Val Lys Ala Val Gly Asn Leu Arg Lys Cys Ser Thr Ser Ser
        675                 680                 685

Leu Leu Glu Ala Cys Thr Phe Arg Arg Pro
    690                 695
```

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 417 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

```
Met Arg Ser Leu Leu Leu Gly Thr Leu Cys Leu Leu Ala Val Ala Leu
1               5                   10                  15

Ala Ala Glu Val Lys Lys Pro Val Glu Ala Ala Ala Pro Gly Thr Ala
            20                  25                  30

Glu Lys Leu Ser Ser Lys Ala Thr Thr Leu Ala Glu Pro Ser Thr Gly
        35                  40                  45

Leu Ala Phe Ser Leu Tyr Gln Ala Met Ala Lys Asp Gln Ala Val Glu
    50                  55                  60

Asn Ile Leu Val Ser Pro Val Val Val Ala Ser Ser Leu Gly Leu Val
65                  70                  75                  80

Ser Leu Gly Gly Lys Ala Thr Thr Ala Ser Gln Ala Lys Ala Val Leu
                85                  90                  95

Ser Ala Glu Gln Leu Arg Asp Glu Glu Val His Ala Gly Leu Gly Glu
            100                 105                 110

Leu Leu Arg Ser Leu Ser Asn Ser Thr Ala Arg Asn Val Thr Trp Lys
        115                 120                 125
```

```
Leu Gly Ser Arg Leu Tyr Gly Pro Ser Ser Val Ser Phe Ala Asp Asp
    130                 135                 140

Phe Val Arg Ser Ser Lys Gln His Tyr Asn Cys Glu His Ser Lys Ile
145                 150                 155                 160

Asn Phe Pro Asp Lys Arg Ser Ala Leu Gln Ser Ile Asn Glu Trp Ala
                165                 170                 175

Ala Gln Thr Thr Asp Gly Lys Leu Pro Glu Val Thr Lys Asp Val Glu
            180                 185                 190

Arg Thr Asp Gly Ala Leu Leu Val Asn Ala Met Phe Phe Lys Pro His
        195                 200                 205

Trp Asp Glu Lys Phe His His Lys Met Val Asp Asn Arg Gly Phe Met
    210                 215                 220

Val Thr Arg Ser Tyr Thr Val Gly Val Thr Met Met His Arg Thr Gly
225                 230                 235                 240

Leu Tyr Asn Tyr Tyr Asp Asp Glu Lys Glu Lys Leu Gln Leu Val Glu
                245                 250                 255

Met Pro Leu Ala His Lys Leu Ser Ser Leu Ile Ile Leu Met Pro His
            260                 265                 270

His Val Glu Pro Leu Glu Arg Leu Glu Lys Leu Leu Thr Lys Glu Gln
        275                 280                 285

Leu Lys Ile Trp Met Gly Lys Met Gln Lys Lys Ala Val Ala Ile Ser
    290                 295                 300

Leu Pro Lys Gly Val Val Glu Val Thr His Asp Leu Gln Lys His Leu
305                 310                 315                 320

Ala Gly Leu Gly Leu Thr Glu Ala Ile Asp Lys Asn Lys Ala Asp Leu
                325                 330                 335
Ser Arg Met Ser Gly Lys Lys Asp Leu Tyr Leu Ala Ser Val Phe His
            340                 345                 350

Ala Thr Ala Phe Glu Leu Asp Thr Asp Gly Asn Pro Phe Asp Gln Asp
        355                 360                 365

Ile Tyr Gly Arg Glu Glu Leu Arg Ser Pro Lys Leu Phe Tyr Ala Asp
    370                 375                 380

His Pro Phe Ile Phe Leu Val Arg Asp Thr Gln Ser Gly Ser Leu Leu
385                 390                 395                 400

Phe Ile Gly Arg Leu Val Arg Leu Lys Gly Asp Lys Met Arg Asp Glu
                405                 410                 415

Leu
```

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 453 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Met Lys Leu Leu Thr Arg Ala Gly Ser Phe Ser Arg Phe Tyr Ser Leu
1 5 10 15

Lys Val Ala Pro Lys Val Lys Ala Thr Ala Ala Pro Ala Gly Ala Pro
20 25 30

Pro Gln Pro Gln Asp Leu Glu Phe Thr Lys Leu Pro Asn Gly Leu Val
35 40 45

Ile Ala Ser Leu Glu Asn Tyr Ser Pro Val Ser Arg Ile Gly Leu Phe
50 55 60

Ile Lys Ala Gly Ser Arg Tyr Glu Asp Phe Ser Asn Leu Gly Thr Thr
65 70 75 80

His Leu Leu Arg Leu Thr Ser Ser Leu Thr Thr Lys Gly Ala Ser Ser
85 90 95

Phe Lys Ile Thr Arg Gly Ile Glu Ala Val Gly Gly Lys Leu Ser Val
100 105 110

Thr Ala Thr Arg Glu Asn Met Ala Tyr Thr Val Glu Cys Leu Arg Gly
115 120 125

Asp Val Asp Ile Leu Met Glu Phe Leu Leu Asn Val Thr Thr Ala Pro
130 135 140

Glu Phe Arg Arg Trp Glu Val Ala Asp Leu Gln Pro Gln Leu Lys Ile
145 150 155 160

Asp Lys Ala Val Ala Phe Gln Asn Pro Gln Thr His Val Ile Glu Asn
165 170 175

Leu His Ala Ala Ala Tyr Gln Asn Ala Leu Ala Asn Pro Leu Tyr Cys
180 185 190

Pro Asp Tyr Arg Ile Gly Lys Val Thr Ser Glu Glu Leu His Tyr Phe
195 200 205

Val Gln Asn His Phe Thr Ser Ala Arg Met Ala Leu Ile Gly Leu Gly
210 215 220

Val Ser His Pro Val Leu Lys Gln Val Ala Glu Gln Phe Leu Asn Met
225 230 235 240

Arg Gly Gly Leu Gly Leu Ser Gly Ala Lys Ala Asn Tyr Arg Gly Gly
245 250 255

Glu Ile Arg Glu Gln Asn Gly Asp Ser Leu Val His Ala Ala Phe Val
260 265 270

Ala Glu Ser Ala Val Ala Gly Ser Ala Glu Ala Asn Ala Phe Ser Val
275 280 285

Leu Gln His Val Leu Gly Ala Gly Pro His Val Lys Arg Gly Ser Asn
290 295 300

Thr Thr Ser His Leu His Gln Ala Val Ala Lys Ala Thr Gln Gln Pro
305 310 315 320

Phe Asp Val Ser Ala Phe Asn Ala Ser Tyr Ser Asp Ser Gly Leu Phe
325 330 335

Gly Ile Tyr Thr Ile Ser Gln Ala Thr Ala Ala Gly Asp Val Ile Lys
340 345 350

Ala Ala Tyr Asn Gln Val Lys Arg Ile Ala Gln Gly Asn Leu Ser Asn
355 360 365

Thr Asp Val Gln Ala Ala Lys Asn Lys Leu Lys Ala Gly Tyr Leu Met
370 375 380

Ser Val Glu Ser Ser Glu Cys Phe Leu Glu Glu Val Gly Ser Gln Ala
385 390 395 400

Leu Val Ala Gly Ser Tyr Met Pro Pro Ser Thr Val Leu Gln Gln Ile
405 410 415

Asp Ser Val Ala Asn Ala Asp Ile Ile Asn Ala Ala Lys Lys Phe Val
420 425 430

Ser Gly Gln Lys Ser Met Ala Ala Ser Gly Asn Leu Gly His Thr Pro
435 440 445

Phe Val Asp Glu Leu
450

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 433 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

Ser Ile Leu Lys Ile His Ala Arg Glu Ile Phe Asp Ser Arg Gly Asn
1 5 10 15

Pro Thr Val Glu Val Asp Leu Phe Thr Ser Lys Gly Leu Phe Arg Ala
20 25 30

Ala Val Pro Ser Gly Ala Ser Thr Gly Ile Tyr Glu Ala Leu Glu Leu
35 40 45

Arg Asp Asn Asp Lys Thr Arg Tyr Met Gly Lys Gly Val Ser Lys Ala
50 55 60

Val Glu His Ile Asn Lys Thr Ile Ala Pro Ala Leu Val Ser Lys Lys
65 70 75 80

Leu Asn Val Thr Glu Gln Glu Lys Ile Asp Lys Leu Met Ile Glu Met
85 90 95

Asp Gly Thr Glu Asn Lys Ser Lys Phe Gly Ala Asn Ala Ile Leu Gly
100 105 110

Val Ser Leu Ala Val Cys Lys Ala Gly Ala Val Glu Lys Gly Val Pro
115 120 125

Leu Tyr Arg His Ile Ala Asp Leu Ala Gly Asn Ser Glu Val Ile Leu
130 135 140

Pro Val Pro Ala Phe Asn Val Ile Asn Gly Gly Ser His Ala Gly Asn
145 150 155 160

Lys Leu Ala Met Gln Glu Phe Met Ile Leu Pro Val Gly Ala Ala Asn
165 170 175

Phe Arg Glu Ala Met Arg Ile Gly Ala Glu Val Tyr His Asn Leu Lys
180 185 190

Asn Val Ile Lys Glu Lys Tyr Gly Lys Asp Ala Thr Asn Val Gly Asp
195 200 205

Glu Gly Gly Phe Ala Pro Asn Ile Leu Glu Asn Lys Glu Gly Leu Glu
210 215 220

Leu Leu Lys Thr Ala Ile Gly Lys Ala Gly Tyr Thr Asp Lys Val Val
225 230 235 240

Ile Gly Met Asp Val Ala Ala Ser Glu Phe Phe Arg Ser Gly Lys Tyr
245 250 255

Asp Leu Asp Phe Lys Ser Pro Asp Asp Pro Ser Arg Tyr Ile Ser Pro
260 265 270

Asp Gln Leu Ala Asp Leu Tyr Lys Ser Phe Ile Lys Asp Tyr Pro Val
275 280 285

Val Ser Ile Glu Asp Pro Phe Asp Gln Asp Asp Trp Gly Ala Trp Gln
290 295 300

Lys Phe Thr Ala Ser Ala Gly Ile Gln Val Val Gly Asp Asp Leu Thr
305 310 315 320

Val Thr Asn Pro Lys Arg Ile Ala Lys Ala Val Asn Glu Lys Ser Cys
325 330 335

Asn Cys Leu Leu Leu Lys Val Asn Gln Ile Gly Ser Val Thr Glu Ser
340 345 350

Leu Gln Ala Cys Lys Leu Ala Gln Ala Asn Gly Trp Gly Val Met Val
355 360 365

Ser His Arg Ser Gly Glu Thr Glu Asp Thr Phe Ile Ala Asp Leu Val
370 375 380

Val Gly Leu Cys Thr Gly Gln Ile Lys Thr Gly Ala Pro Cys Arg Ser
385 390 395 400

Glu Arg Leu Ala Lys Tyr Asn Gln Leu Leu Arg Ile Glu Glu Glu Leu
405 410 415

Gly Ser Lys Ala Lys Phe Ala Gly Arg Asn Phe Arg Asn Pro Leu Ala
420 425 430

Lys

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 417 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

Ser Leu Ser Asn Lys Leu Thr Leu Asp Lys Leu Asp Val Lys Gly Lys
1 5 10 15

Arg Val Val Met Arg Val Asp Phe Asn Val Pro Met Lys Asn Asn Gln
20 25 30

Ile Thr Asn Asn Gln Arg Ile Lys Ala Ala Val Pro Ser Ile Lys Phe
35 40 45

Cys Leu Asp Asn Gly Ala Lys Ser Val Val Leu Met Ser His Leu Gly
50 55 60

Arg Pro Asp Gly Val Pro Met Pro Asp Lys Tyr Ser Leu Glu Pro Val
65 70 75 80

Ala Val Glu Leu Lys Ser Leu Leu Gly Lys Asp Val Leu Phe Leu Lys
85 90 95

Asp Cys Val Gly Pro Glu Val Glu Lys Ala Cys Ala Asn Pro Ala Ala
100 105 110

Gly Ser Val Ile Leu Leu Glu Asn Leu Arg Phe His Val Glu Glu Glu
115 120 125

Gly Lys Gly Lys Asp Ala Ser Gly Asn Lys Val Lys Ala Glu Pro Ala
130 135 140

Lys Ile Glu Ala Phe Arg Ala Ser Leu Ser Lys Leu Gly Asp Val Tyr
145 150 155 160

Val Asn Asp Ala Phe Gly Thr Ala His Arg Ala His Ser Ser Met Val
165 170 175

Gly Val Asn Leu Pro Gln Lys Ala Gly Gly Phe Leu Met Lys Lys Glu
180 185 190

Leu Asn Tyr Phe Ala Lys Ala Leu Glu Ser Pro Glu Arg Pro Phe Leu
195 200 205

Ala Ile Leu Gly Gly Ala Lys Val Ala Asp Lys Ile Gln Leu Ile Asn
210 215 220

Asn Met Leu Asp Lys Val Asn Glu Met Ile Ile Gly Gly Gly Met Ala
225 230 235 240

Phe Thr Phe Leu Lys Val Leu Asn Asn Met Glu Ile Gly Thr Ser Leu
245 250 255

Phe Asp Glu Glu Gly Ala Lys Ile Val Lys Asp Leu Met Ser Lys Ala
260 265 270

Glu Lys Asn Gly Val Lys Ile Thr Leu Pro Val Asp Phe Val Thr Ala
275 280 285

Asp Lys Phe Asp Glu Asn Ala Lys Thr Gly Gln Ala Thr Val Ala Ser
290 295 300

Gly Ile Pro Ala Gly Trp Met Gly Leu Asp Cys Gly Pro Glu Ser Ser
305 310 315 320

Lys Lys Tyr Ala Glu Ala Val Thr Arg Ala Lys Gln Ile Val Trp Asn
325 330 335

Gly Pro Val Gly Val Phe Glu Trp Glu Ala Phe Ala Arg Gly Thr Lys
340 345 350

Ala Leu Met Asp Glu Val Val Lys Ala Thr Ser Arg Gly Cys Ile Thr
355 360 365

Ile Ile Gly Gly Gly Asp Thr Ala Thr Cys Cys Ala Lys Trp Asn Thr
370 375 380

Glu Asp Lys Val Ser His Val Ser Thr Gly Gly Gly Ala Ser Leu Glu
385 390 395 400

Leu Leu Glu Gly Lys Val Leu Pro Gly Val Asp Ala Leu Ser Asn Ile
405 410 415

Leu

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 249 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

Met Ala Pro Ser Arg Lys Phe Phe Val Gly Gly Asn Trp Lys Met Asn
1 5 10 15

Gly Arg Lys Gln Ser Leu Gly Glu Leu Ile Gly Thr Leu Asn Ala Ala
20 25 30

Lys Val Pro Ala Asp Thr Glu Val Val Cys Ala Pro Pro Thr Ala Tyr
35 40 45

Ile Asp Phe Ala Arg Gln Lys Leu Asp Pro Lys Ile Ala Val Ala Ala
50 55 60

Gln Asn Cys Tyr Lys Val Thr Asn Gly Ala Phe Thr Gly Glu Ile Ser
65 70 75 80

Pro Gly Met Ile Lys Asp Cys Gly Ala Thr Trp Val Val Leu Gly His
85 90 95

Ser Glu Arg Arg His Val Phe Gly Glu Ser Asp Glu Leu Ile Gly Gln
100 105 110

Lys Val Ala His Ala Leu Ala Glu Gly Leu Gly Val Ile Ala Cys Ile
115 120 125

Gly Glu Lys Leu Asp Glu Arg Glu Ala Gly Ile Thr Glu Lys Val Val
130 135 140

Phe Glu Gln Thr Lys Val Ile Ala Asp Asn Val Lys Asp Trp Ser Lys
145 150 155 160

Val Val Leu Ala Tyr Glu Pro Val Trp Ala Ile Gly Thr Gly Lys Thr
165 170 175

Ala Thr Pro Gln Gln Ala Gln Glu Val His Glu Lys Leu Arg Gly Trp
180 185 190

Leu Lys Ser Asn Val Ser Asp Ala Val Ala Gln Ser Thr Arg Ile Ile
195 200 205

Tyr Gly Gly Ser Val Thr Gly Ala Thr Cys Lys Glu Leu Ala Ser Gln
210 215 220

Pro Asp Val Asp Gly Phe Leu Val Gly Gly Ala Ser Leu Lys Pro Glu
225 230 235 240

Phe Val Asp Ile Ile Asn Ala Lys Gln
245

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1076 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

Pro Val Pro Leu Ser Phe Leu Ser Thr Val Cys Asp Pro Arg Val Gln
1 5 10 15

Asp Gly Ala Ala Glu Arg Thr Gly Ala Ala Asp Gly Glu Glu Phe Leu
20 25 30

Gly Gly Gly Gly Leu Pro Ala Glu Leu Phe Gln Lys Lys Val Val Ala
35 40 45

Ser Phe Pro Arg Thr Val Leu Ser Thr Gly Met Asp Asn Arg Tyr Leu
50 55 60

Val Leu Ala Val Asn Thr Val Gln Asn Lys Glu Gly Asn Cys Glu Lys
65 70 75 80

Arg Leu Val Ile Thr Ala Ser Gln Ser Leu Glu Asn Lys Glu Leu Cys
85 90 95

Ile Leu Arg Asn Asp Trp Cys Ser Val Pro Val Glu Pro Gly Asp Ile
100 105 110

Ile His Leu Glu Gly Asp Cys Thr Ser Asp Thr Trp Ile Ile Asp Lys
115 120 125

Asp Phe Gly Tyr Leu Ile Leu Tyr Pro Asp Met Leu Ile Ser Gly Thr
130 135 140

Ser Ile Ala Ser Ser Ile Arg Cys Met Arg Arg Ala Val Leu Ser Glu
145 150 155 160

Thr Phe Arg Ser Ser Asp Pro Ala Thr Arg Gln Met Leu Ile Gly Thr
165 170 175

Val Leu His Glu Val Phe Gln Lys Ala Ile Asn Asn Ser Phe Ala Pro
180 185 190

Glu Lys Leu Gln Glu Leu Ala Phe Gln Thr Ile Gln Glu Ile Arg His
195 200 205

Leu Lys Glu Met Tyr Arg Leu Asn Leu Ser Gln Asp Glu Ile Lys Gln
210 215 220

Glu Val Glu Asp Tyr Leu Pro Ser Phe Cys Lys Trp Ala Gly Asp Phe
225 230 235 240

Met His Lys Asn Thr Ser Thr Asp Phe Pro Gln Met Gln Leu Ser Leu
245 250 255

Pro Ser Asp Asn Ser Lys Asp Asn Ser Thr Cys Asn Ile Glu Val Val
260 265 270

Lys Pro Met Asp Ile Glu Glu Ser Ile Trp Ser Pro Arg Phe Gly Leu
275 280 285

Lys Gly Lys Ile Asp Val Thr Val Gly Val Lys Ile His Arg Gly Tyr
290 295 300

Lys Thr Lys Tyr Lys Ile Met Pro Leu Glu Leu Lys Thr Gly Lys Glu
305 310 315 320

Ser Asn Ser Ile Glu His Arg Ser Gln Val Val Leu Tyr Thr Leu Leu
325 330 335

Ser Gln Glu Arg Arg Ala Asp Pro Glu Ala Gly Leu Leu Leu Tyr Leu
340 345 350

Lys Thr Gly Gln Met Tyr Pro Val Pro Ala Asn His Leu Asp Lys Arg
355 360 365

Glu Leu Leu Lys Leu Arg Asn Gln Met Ala Phe Ser Leu Phe His Arg
370 375 380

Ile Ser Lys Ser Ala Thr Arg Gln Lys Thr Gln Leu Ala Ser Leu Pro
385 390 395 400

Gln Ile Ile Glu Glu Glu Lys Thr Cys Lys Tyr Cys Ser Gln Ile Gly
405 410 415

Asn Cys Ala Leu Tyr Ser Arg Ala Val Glu Gln Gln Met Asp Cys Ser
420 425 430

Ser Val Pro Ile Val Met Leu Pro Lys Ile Glu Glu Glu Thr Gln His
435 440 445

Leu Lys Gln Thr His Leu Glu Tyr Phe Ser Leu Trp Cys Leu Met Leu
450 455 460

Thr Leu Glu Ser Gln Ser Lys Asp Asn Lys Lys Asn His Gln Asn Ile
465 470 475 480

Trp Leu Met Pro Ala Ser Glu Met Glu Lys Ser Gly Ser Cys Ile Gly
485 490 495

Asn Leu Ile Arg Met Glu His Val Lys Ile Val Cys Asp Gly Gln Tyr
500 505 510

Leu His Asn Phe Gln Cys Lys His Gly Ala Ile Pro Val Thr Asn Leu
515 520 525

Met Ala Gly Asp Arg Val Ile Val Ser Gly Glu Glu Arg Ser Leu Phe
530 535 540

Ala Leu Ser Arg Gly Tyr Val Lys Glu Ile Asn Met Thr Thr Val Thr
545 550 555 560

Cys Leu Leu Asp Arg Asn Leu Ser Val Leu Pro Glu Ser Thr Leu Phe
565 570 575

Arg Leu Asp Gln Glu Glu Lys Asn Cys Asp Ile Asp Thr Pro Leu Gly
580 585 590

Asn Leu Ser Lys Leu Met Glu Asn Thr Phe Val Ser Lys Lys Leu Arg
595 600 605

Asp Leu Ile Ile Asp Phe Arg Glu Pro Gln Phe Ile Ser Tyr Leu Ser
610 615 620

Ser Val Leu Pro His Asp Ala Lys Asp Thr Val Ala Cys Ile Leu Lys
625 630 635 640

Gly Leu Asn Lys Pro Gln Arg Gln Ala Met Lys Lys Val Leu Leu Ser
645 650 655

Lys Asp Tyr Thr Leu Ile Val Gly Met Pro Gly Thr Gly Lys Thr Thr
660 665 670

Thr Ile Cys Thr Leu Val Arg Ile Leu Tyr Ala Cys Gly Phe Ser Val
675 680 685

Leu Leu Thr Ser Tyr Thr His Ser Ala Val Asp Asn Ile Leu Leu Lys
690 695 700

Leu Ala Lys Phe Lys Ile Gly Phe Leu Arg Leu Gly Gln Ile Gln Lys
705 710 715 720

Val His Pro Ala Ile Gln Gln Phe Thr Glu Gln Glu Ile Cys Arg Ser
725 730 735

Lys Ser Ile Lys Ser Leu Ala Leu Leu Glu Glu Leu Tyr Asn Ser Gln
740 745 750

Leu Ile Val Ala Thr Thr Cys Met Gly Ile Asn His Pro Ile Phe Ser
755 760 765

Arg Lys Ile Phe Asp Phe Cys Ile Val Asp Glu Ala Ser Gln Ile Ser
770 775 780

Gln Pro Ile Cys Leu Gly Pro Leu Phe Phe Ser Arg Arg Phe Val Leu
785 790 795 800

Val Gly Asp His Gln Gln Leu Pro Pro Leu Val Leu Asn Arg Glu Ala
805 810 815

Arg Ala Leu Gly Met Ser Glu Ser Leu Phe Lys Arg Leu Glu Gln Asn
820 825 830

Lys Ser Ala Val Val Gln Leu Thr Val Gln Tyr Arg Met Asn Ser Lys
835 840 845

Ile Met Ser Leu Ser Asn Lys Leu Thr Tyr Glu Gly Lys Leu Glu Cys
850 855 860

Gly Ser Asp Lys Val Ala Asn Ala Val Ile Asn Leu Arg His Phe Lys
865 870 875 880

Asp Val Lys Leu Glu Leu Glu Phe Tyr Ala Asp Tyr Ser Asp Asn Pro
885 890 895

Trp Leu Met Gly Val Phe Glu Pro Asn Asn Pro Val Cys Phe Leu Asn
900 905 910

Thr Asp Lys Val Pro Ala Pro Glu Gln Val Glu Lys Gly Gly Val Ser
915 920 925

Asn Val Thr Glu Ala Lys Leu Ile Val Phe Leu Thr Ser Ile Phe Val
930 935 940

Lys Ala Gly Cys Ser Pro Ser Asp Ile Gly Ile Ile Ala Pro Tyr Arg
945 950 955 960

Gln Gln Leu Lys Ile Ile Asn Asp Leu Leu Ala Arg Ser Ile Gly Met
965 970 975

Val Glu Val Asn Thr Val Asp Lys Tyr Gln Gly Arg Asp Lys Ser Ile
980 985 990

Val Leu Val Ser Phe Val Arg Ser Asn Lys Asp Gly Thr Val Gly Glu
995 1000 1005

Leu Leu Lys Asp Trp Arg Arg Leu Asn Val Ala Ile Thr Arg Ala Lys
1010 1015 1020

His Lys Leu Ile Leu Leu Gly Cys Val Pro Ser Leu Asn Cys Tyr Pro
1025 1030 1035 1040

Pro Leu Glu Lys Leu Leu Asn His Leu Asn Ser Glu Lys Leu Ile Ile
1045 1050 1055

Asp Leu Pro Ser Arg Glu His Glu Ser Leu Cys His Ile Leu Gly Asp
1060 1065 1070

Phe Gln Arg Glu
1075

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 527 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

Met Ala Asp Ser Arg Asp Pro Ala Ser Asp Gln Met Gln His Trp Lys
1 5 10 15

Glu Gln Arg Ala Ala Gln Lys Ala Asp Val Leu Thr Thr Gly Ala Gly
20 25 30

Asn Pro Val Gly Asp Lys Leu Asn Val Ile Thr Val Gly Pro Arg Gly
35 40 45

Pro Leu Leu Val Gln Asp Val Val Phe Thr Asp Glu Met Ala His Phe
50 55 60

Asp Arg Glu Arg Ile Pro Glu Arg Val Val His Ala Lys Gly Ala Gly
65 70 75 80

Ala Phe Gly Tyr Phe Glu Val Thr His Asp Ile Thr Lys Tyr Ser Lys
85 90 95

Ala Lys Val Phe Glu His Ile Gly Lys Lys Thr Pro Ile Ala Val Arg
100 105 110

Phe Ser Thr Val Ala Gly Glu Ser Gly Ser Ala Asp Thr Val Arg Asp
115 120 125

Pro Arg Gly Phe Ala Val Lys Phe Tyr Thr Glu Asp Gly Asn Trp Asp
130 135 140

Leu Val Gly Asn Asn Thr Pro Ile Phe Phe Ile Arg Asp Pro Ile Leu
145 150 155 160

Phe Pro Ser Phe Ile His Ser Gln Lys Arg Asn Pro Gln Thr His Leu
165 170 175

Lys Asp Pro Asp Met Val Trp Asp Phe Trp Ser Leu Arg Pro Glu Ser
180 185 190

Leu His Gln Val Ser Phe Leu Phe Ser Asp Arg Gly Ile Pro Asp Gly
195 200 205

His Arg His Met Asn Gly Tyr Gly Ser His Thr Phe Lys Leu Val Asn
210 215 220

Ala Asn Gly Glu Ala Val Tyr Cys Lys Phe His Tyr Lys Thr Asp Gln
225 230 235 240

Gly Ile Lys Asn Leu Ser Val Glu Asp Ala Ala Arg Leu Ser Gln Glu
245 250 255

Asp Pro Asp Tyr Gly Ile Arg Asp Leu Phe Asn Ala Ile Ala Thr Gly
260 265 270

Lys Tyr Pro Ser Trp Thr Phe Tyr Ile Gln Val Met Thr Phe Asn Gln
275 280 285

Ala Glu Thr Phe Pro Phe Asn Pro Phe Asp Leu Thr Lys Val Trp Pro
290 295 300

His Lys Asp Tyr Pro Leu Ile Pro Val Gly Lys Leu Val Leu Asn Arg
305 310 315 320

Asn Pro Val Asn Tyr Phe Ala Glu Val Glu Gln Ile Ala Phe Asp Pro
325 330 335

Ser Asn Met Pro Pro Gly Ile Glu Ala Ser Pro Asp Lys Met Leu Gln
340 345 350

Gly Arg Leu Phe Ala Tyr Pro Asp Thr His Arg His Arg Leu Gly Pro
355 360 365

Asn Tyr Leu His Ile Pro Val Asn Cys Pro Tyr Arg Ala Arg Val Ala
370 375 380

Asn Tyr Gln Arg Asp Gly Pro Met Cys Met Gln Asp Asn Gln Gly Gly
385 390 395 400

Ala Pro Asn Tyr Tyr Pro Asn Ser Phe Gly Ala Pro Glu Gln Gln Pro
405 410 415

Ser Ala Leu Glu His Ser Ile Gln Tyr Ser Gly Glu Val Arg Arg Phe
420 425 430

Asn Thr Ala Asn Asp Asp Asn Val Thr Gln Val Arg Ala Phe Tyr Val
435 440 445

Asn Val Leu Asn Glu Glu Gln Arg Lys Arg Leu Cys Glu Asn Ile Ala
450 455 460

Gly His Leu Lys Asp Ala Gln Ile Phe Ile Gln Lys Lys Ala Val Lys
465 470 475 480

Asn Phe Thr Glu Val His Pro Asp Tyr Gly Ser His Ile Gln Ala Leu
485 490 495

Leu Asp Lys Tyr Asn Ala Glu Lys Pro Lys Asn Ala Ile His Thr Phe
500 505 510

Val Gln Ser Gly Ser His Leu Ala Ala Arg Glu Lys Ala Asn Leu
515 520 525

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 353 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

Met Glu Lys Thr Leu Glu Thr Val Pro Leu Glu Arg Lys Lys Arg Glu
1 5 10 15

Lys Glu Gln Phe Arg Lys Leu Phe Ile Gly Gly Leu Ser Phe Glu Thr
20 25 30

Thr Glu Glu Ser Leu Arg Asn Tyr Tyr Glu Gln Trp Gly Lys Leu Thr
35 40 45

Asp Cys Val Val Met Arg Asp Pro Ala Ser Lys Arg Ser Arg Gly Phe
50 55 60

Gly Phe Val Thr Phe Ser Ser Met Ala Glu Val Asp Ala Ala Met Ala
65 70 75 80

Ala Arg Pro His Ser Ile Asp Gly Arg Val Val Glu Pro Lys Arg Ala
85 90 95

Val Ala Arg Glu Glu Ser Gly Lys Pro Gly Ala His Val Thr Val Lys
100 105 110

Lys Leu Phe Val Gly Gly Ile Lys Glu Asp Thr Glu Glu His His Leu
115 120 125

Arg Asp Tyr Phe Glu Glu Tyr Gly Lys Ile Asp Thr Ile Glu Ile Ile
130 135 140

Thr Asp Arg Gln Ser Gly Lys Lys Arg Gly Phe Gly Phe Val Thr Phe
145 150 155 160

Asp Asp His Asp Pro Val Asp Lys Ile Val Leu Gln Lys Tyr His Thr
165 170 175

Ile Asn Gly His Asn Ala Glu Val Arg Lys Ala Leu Ser Arg Gln Glu
180 185 190

Met Gln Glu Val Gln Ser Ser Arg Ser Gly Arg Gly Gly Asn Phe Gly
195 200 205

Phe Gly Asp Ser Arg Gly Gly Gly Gly Asn Phe Gly Pro Gly Pro Gly
210 215 220

Ser Asn Phe Arg Gly Gly Ser Asp Gly Tyr Gly Ser Gly Arg Gly Phe
225 230 235 240

Gly Asp Gly Tyr Asn Gly Tyr Gly Gly Gly Pro Gly Gly Gly Asn Phe
245 250 255

Gly Gly Ser Pro Gly Tyr Gly Gly Gly Arg Gly Gly Tyr Gly Gly Gly
260 265 270

Gly Pro Gly Tyr Gly Asn Gln Gly Gly Gly Tyr Gly Gly Gly Tyr Asp
275 280 285

Asn Tyr Gly Gly Gly Asn Tyr Gly Ser Gly Asn Tyr Asn Asp Phe Gly
290 295 300

Asn Tyr Asn Gln Gln Pro Ser Asn Tyr Gly Pro Met Lys Ser Gly Asn
305 310 315 320

Phe Gly Gly Ser Arg Asn Met Gly Gly Pro Tyr Gly Gly Gly Asn Tyr
325 330 335

Gly Pro Gly Gly Ser Gly Gly Ser Gly Gly Tyr Gly Gly Arg Ser Arg
340 345 350

Tyr

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 194 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

Met Ala Ala Glu Asp Val Ala Ala Thr Gly Ala Asp Pro Ser Glu Leu
1 5 10 15

Glu Gly Gly Gly Leu Leu His Glu Ile Phe Thr Ser Pro Leu Asn Leu
20 25 30

Leu Leu Leu Gly Leu Cys Ile Phe Leu Leu Tyr Lys Ile Val Arg Gly
35 40 45

Asp Gln Pro Ala Ala Ser Asp Ser Asp Asp Asp Glu Pro Pro Pro Leu
50 55 60

Pro Arg Leu Lys Arg Arg Asp Phe Thr Pro Ala Glu Leu Arg Arg Phe
65 70 75 80

Asp Gly Val Gln Asp Pro Arg Ile Leu Met Ala Ile Asn Gly Lys Val
85 90 95

Phe Asp Val Thr Lys Gly Arg Lys Phe Tyr Gly Pro Glu Gly Pro Tyr
100 105 110

Gly Val Phe Ala Gly Arg Asp Ala Ser Arg Gly Leu Ala Thr Phe Cys
115 120 125

Leu Asp Lys Glu Ala Leu Lys Asp Glu Tyr Asp Asp Leu Ser Asp Leu
130 135 140

Thr Pro Ala Gln Gln Glu Thr Leu Asn Asp Trp Asp Ser Gln Phe Thr
145 150 155 160

Phe Lys Tyr His His Val Gly Lys Leu Leu Lys Glu Gly Glu Glu Pro
165 170 175

Thr Val Tyr Ser Asp Glu Glu Glu Pro Lys Asp Glu Ser Ala Arg Lys
180 185 190

Asn Asp

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 646 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

Met Ser Lys Gly Pro Ala Val Gly Ile Asp Leu Gly Thr Thr Tyr Ser
1 5 10 15

Cys Val Gly Val Phe Gln His Gly Lys Val Glu Ile Ile Ala Asn Asp
20 25 30

Gln Gly Asn Arg Thr Thr Pro Ser Tyr Val Ala Phe Thr Asp Thr Glu
35 40 45

Arg Leu Ile Gly Asp Ala Ala Lys Asn Gln Val Ala Met Asn Pro Thr
50 55 60

Asn Thr Val Phe Asp Ala Lys Arg Leu Ile Gly Arg Arg Phe Asp Asp
65 70 75 80

Ala Val Val Gln Ser Asp Met Lys His Trp Pro Phe Met Val Val Asn
85 90 95

Asp Ala Gly Arg Pro Lys Val Gln Val Glu Tyr Lys Gly Glu Thr Lys
100 105 110

Ser Phe Tyr Pro Glu Glu Val Ser Ser Met Val Leu Thr Lys Met Lys
115 120 125

Glu Ile Ala Glu Ala Tyr Leu Gly Lys Thr Val Thr Asn Ala Val Val
130 135 140

Thr Val Pro Ala Tyr Phe Asn Asp Ser Gln Arg Gln Ala Thr Lys Asp
145 150 155 160

Ala Gly Thr Ile Ala Gly Leu Asn Val Leu Arg Ile Ile Asn Glu Pro
165 170 175

Thr Ala Ala Ala Ile Ala Tyr Gly Leu Asp Lys Lys Val Gly Ala Glu
180 185 190

Arg Asn Val Leu Ile Phe Asp Leu Gly Gly Gly Thr Phe Asp Val Ser
195 200 205

Ile Leu Thr Ile Glu Asp Gly Ile Phe Glu Val Lys Ser Thr Ala Gly
210 215 220

Asp Thr His Leu Gly Gly Glu Asp Phe Asp Asn Arg Met Val Asn His
225 230 235 240

Phe Ile Ala Glu Phe Lys Arg Lys His Lys Lys Asp Ile Ser Glu Asn
245 250 255

Lys Arg Ala Val Arg Arg Leu Arg Thr Ala Cys Glu Arg Ala Lys Arg
260 265 270

Thr Leu Ser Ser Ser Thr Gln Ala Ser Ile Glu Ile Asp Ser Leu Tyr
275 280 285

Glu Gly Ile Asp Phe Tyr Thr Ser Ile Thr Arg Ala Arg Phe Glu Glu
290 295 300

Leu Asn Ala Asp Leu Phe Arg Gly Thr Leu Asp Pro Val Glu Lys Ala
305 310 315 320

Leu Arg Asp Ala Lys Leu Asp Lys Ser Gln Ile His Asp Ile Val Leu
325 330 335

Val Gly Gly Ser Thr Arg Ile Pro Lys Ile Gln Lys Leu Leu Gln Asp
340 345 350

Phe Phe Asn Gly Lys Glu Leu Asn Lys Ser Ile Asn Pro Asp Glu Ala
355 360 365

Val Ala Tyr Gly Ala Ala Val Gln Ala Ala Ile Leu Ser Gly Asp Lys
370 375 380

Ser Glu Asn Val Gln Asp Leu Leu Leu Leu Asp Val Thr Pro Leu Ser
385 390 395 400

Leu Gly Ile Glu Thr Ala Gly Gly Val Met Thr Val Leu Ile Lys Arg
405 410 415

Asn Thr Thr Ile Pro Thr Lys Gln Thr Gln Thr Phe Thr Thr Tyr Ser
420 425 430

Asp Asn Gln Pro Gly Val Leu Ile Gln Val Tyr Glu Gly Glu Arg Ala
435 440 445

Met Thr Lys Asp Asn Asn Leu Leu Gly Lys Phe Glu Leu Thr Gly Ile
450 455 460

Pro Pro Ala Pro Arg Gly Val Pro Gln Ile Glu Val Thr Phe Asp Ile
465 470 475 480

Asp Ala Asn Gly Ile Leu Asn Val Ser Ala Val Asp Lys Ser Thr Gly
485 490 495

Lys Glu Asn Lys Ile Thr Ile Thr Asn Asp Lys Gly Arg Leu Ser Lys
500 505 510

Glu Asp Ile Glu Arg Met Val Gln Glu Ala Glu Lys Tyr Lys Ala Glu
515 520 525

Asp Glu Lys Gln Arg Asp Lys Val Ser Ser Lys Asn Ser Leu Glu Ser
530 535 540

Tyr Ala Phe Asn Met Lys Ala Thr Val Glu Asp Glu Lys Leu Gln Gly
545 550 555 560

Lys Ile Asn Asp Glu Asp Lys Gln Lys Ile Leu Asp Lys Cys Asn Glu
565 570 575

Ile Ile Asn Trp Leu Asp Lys Asn Gln Thr Ala Glu Lys Glu Glu Phe
580 585 590

Glu His Gln Gln Lys Glu Leu Glu Lys Val Cys Asn Pro Ile Ile Thr
595 600 605

Lys Leu Tyr Gln Ser Ala Gly Gly Met Pro Gly Gly Met Pro Gly Gly
610 615 620

Phe Pro Gly Gly Gly Ala Pro Pro Ser Gly Gly Ala Ser Ser Gly Pro
625 630 635 640

Thr Ile Glu Glu Val Asp
645

CLAIMS

1. A method of characterising a biological sample comprising detecting or quantitating therein one or more proteins produced by the endometrium in increased amounts in hyperplasia or in adenocarcinoma as shown by 2D gel electrophoresis comparison of cell lysates of endometrial biopsies from normal endometrium and endometrium showing hyperplasia or adenocarcinoma, excluding variations due to the menstrual cycle, or detecting or quantitating a fragment or breakdown product thereof, or a nucleic acid coding therefor or antibodies thereto.

2. A method of characterising a biological sample comprising detecting or quantitating therein one or more proteins produced by the endometrium in increased amounts in hyperplasia or in adenocarcinoma and characterised by one of the following combinations of molecular weight and pI values:

hyperplasia	
pI	MW kDa
6.7	91
6.6	90
6.9	64
6.6	67
6.3	66
6.8	46
5.7	41
5.5	35
5.3	13
6.6	101
5.8	14
7.4	51
8.2	44
9.5	48

	adenocarcinoma	
	pI	MW (kDa)
	6.3	32
	6.0	109
	6.7	91
	6.6	90
	6.9	64
	6.6	67
	6.3	66
	6.2	62
	6.2	45
	5.7	45
	5.4	33
	6.3	27
	6.5	103
	6.8	90
	6.9	78
	5.3	13
	6.2	130
	6.3	66
	6.3	73
	8.3	32
	8.1	55
	8.2	44
	6.6	111
	7.7	43
	9.5	48
	8.3	32
	7.7	39

or a fragment or breakdown product thereof, or a nucleic acid coding therefor or antibodies thereto.

3. A method as claimed in Claim 1 or Claim 2, wherein said protein, fragment, breakdown product, antibodies, or nucleic acid is detected in a body fluid sample.

4. An immunological binding partner specifically reactive with a protein as defined in Claim 1 or Claim 2 or with a fragment or breakdown product thereof or with a nucleic acid coding therefor.

5. A cell line producing a monoclonal antibody being an immunological binding partner as claimed in Claim 4.

6. An assay kit for use in a method as claimed in Claim 1 or Claim 2, comprising an immunological binding partner as claimed in Claim 4.

7. A method of characterising a biological sample comprising detecting or quantitating therein one or more proteins produced by the endometrium in increased amounts during the proliferative phase of the endometrium as shown in 2D gel electrophoresis comparison of cell lysates of endometrial biopsies from normal endometrium in its proliferative and secretory phases and characterised by one of the following combinations of molecular weight and pI values:-

pI	MW(kDa)
6.9	86
5.4	34
5.6	67
5.3	23
6.8	52
8.7	47
8.2	138
6.5	124
7.7	119
7.8	119
8.1	66
7.1	58
6.8	66
7.9	48
7.7	31
6.8	29
7.2	70
8.0	119
6.7	62

or a fragment or breakdown product thereof, or a nucleic acid coding therefor, or an antibody thereto.

8. A method as claimed in Claim 7, for detecting the phase of the endometrium.

9. A method as claimed in Claim 7 or Claim 8, wherein said protein, fragment, or breakdown product is detected in a body fluid sample.

10. An immunological binding partner specifically reactive with a protein as defined in Claim 7 or with a fragment or breakdown product thereof or with a nucleic acid coding therefor.

11. A cell line producing a monoclonal antibody being an immunological binding partner as claimed in Claim 10.

12. An assay kit for use in a method as claimed in Claim 7 or Claim 8, comprising an immunological binding partner as claimed in Claim 10.

13. A protein produced by the endometrium in increased amounts in hyperplasia or in adenocarcinoma as shown by 2D gel electrophoresis comparison of cell lysates of endo-metrial biopsies from normal endometrium and endometrium showing hyperplasia or adenocarcinoma, excluding variations due to the menstrual cycle, and characterised by one of the following combinations of molecular weight and pI values:

hyperplasia	
pI	MW kDa
6.7	91
6.6	90
6.9	64
6.8	46
5.7	41
5.3	13
6.6	101
5.8	14
9.5	48

adenocarcinoma	
pI	MW (kDa)
6.3	32
6.0	109
6.7	91
6.6	90
6.9	64
6.2	62
6.5	103
6.8	90
5.3	13
6.2	130
6.3	66
6.3	73
8.3	32
8.1	55
6.6	111
7.7	43
9.5	48
8.3	32

14. A protein produced by the endometrium in increased amounts during the proliferative phase of the endometrium as shown in 2D gel electrophoresis comparison of cell lysates of endometrial biopsies from normal endometrium in its proliferative and secretory phases and characterised by one of the following combinations of molecular weight and pI values:-

pI	MW(kDa)
6.9	86
5.6	67
6.8	52
8.2	138
6.5	124
7.7	119
7.8	119
8.1	66
7.1	58
6.8	66
7.7	31

15. A protein as claimed in Claim 13 or Claim 14, characterised by the properties:-

PI	MW(kDa)
5.7	41
5.6	67
9.5	48
6.8	52
6.5	124
7.7	119
7.8	119

and by the respective tryptic digestion MS spectra shown in Figures 7 to 12.

16. The use of a protein as defined in any one of Claims 1, 2 or 7 or a fragment thereof, for detecting autoantibodies to a said protein.

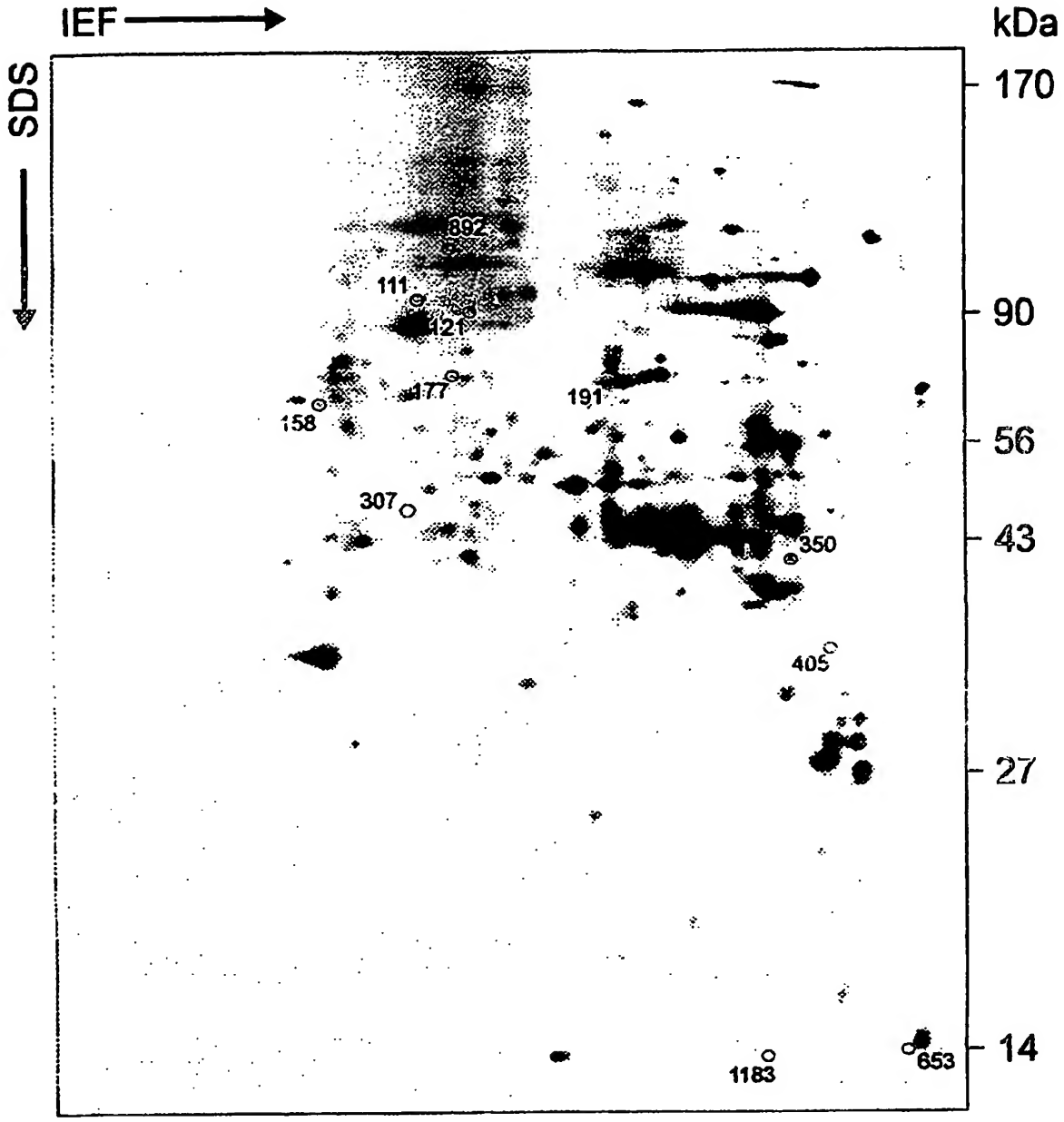

IEF
SDS
kDa
170
90
56
43
27
14
392
111
121
177
158
191
307
350
405
1183
653

FIG. 1

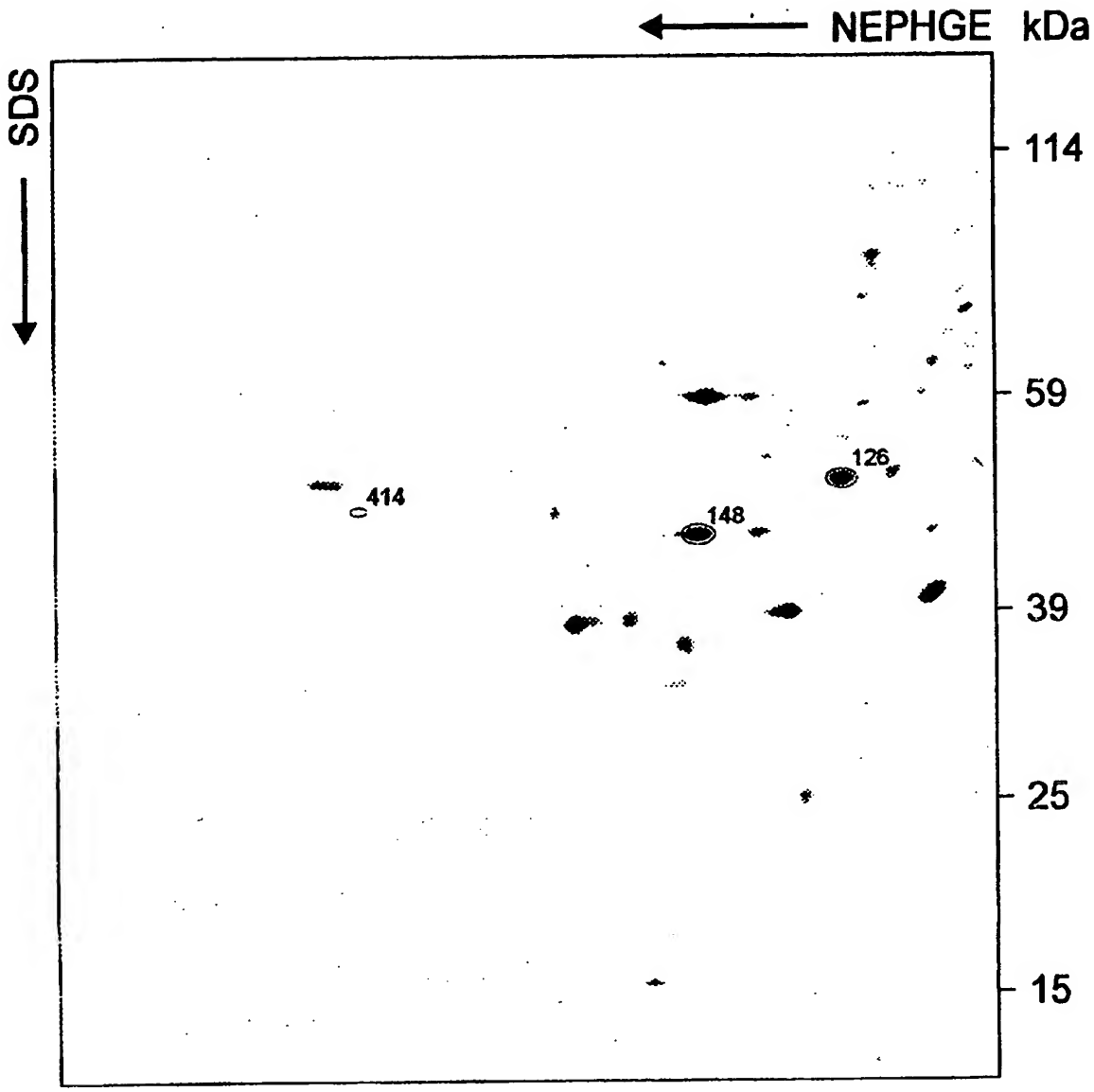


FIG. 2

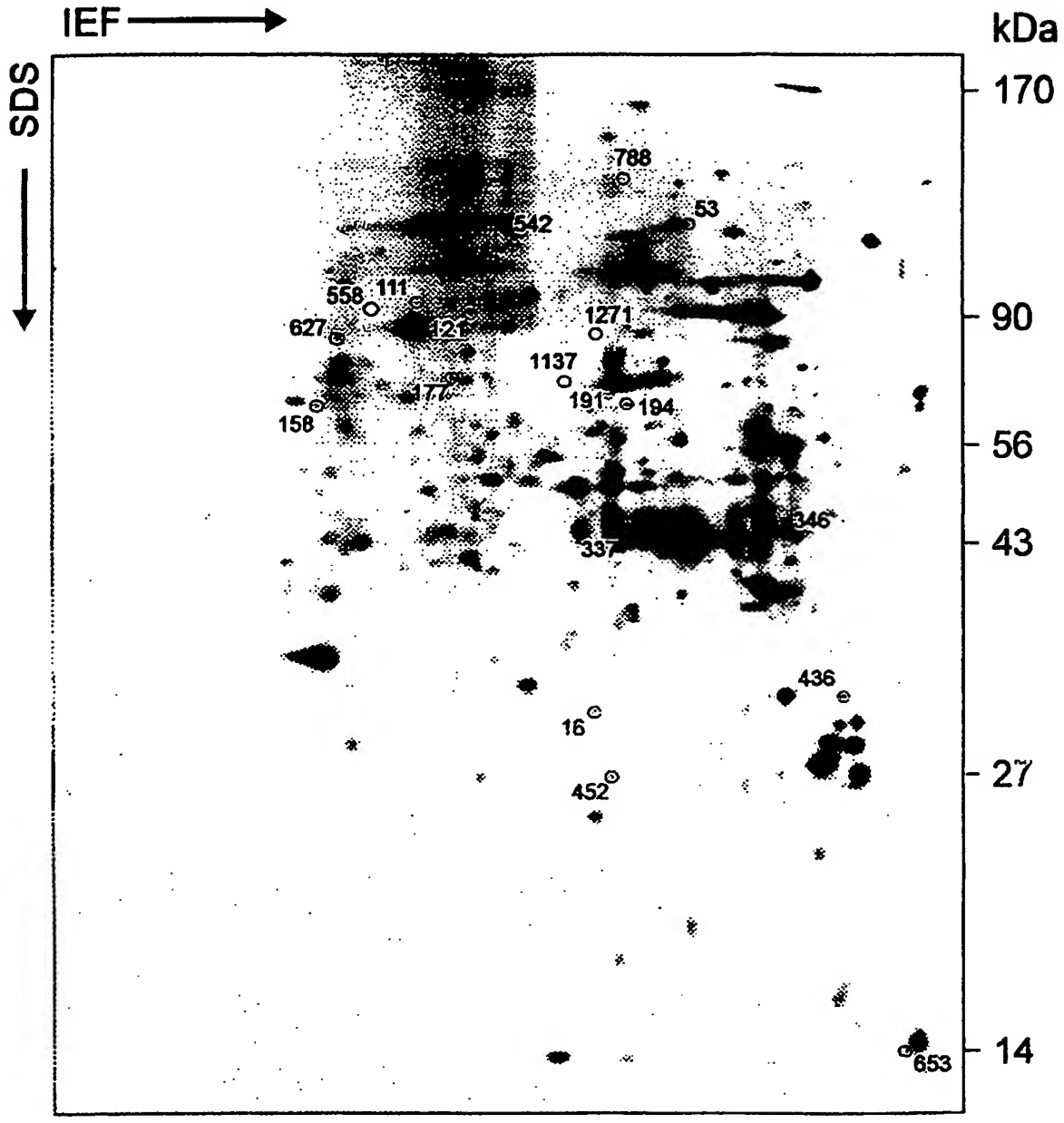

IEF
SDS
kDa
170
90
56
43
27
14
788
53
542
558
111
627
121
1271
1137
191
194
158
346
337
436
16
452
653

FIG. 3

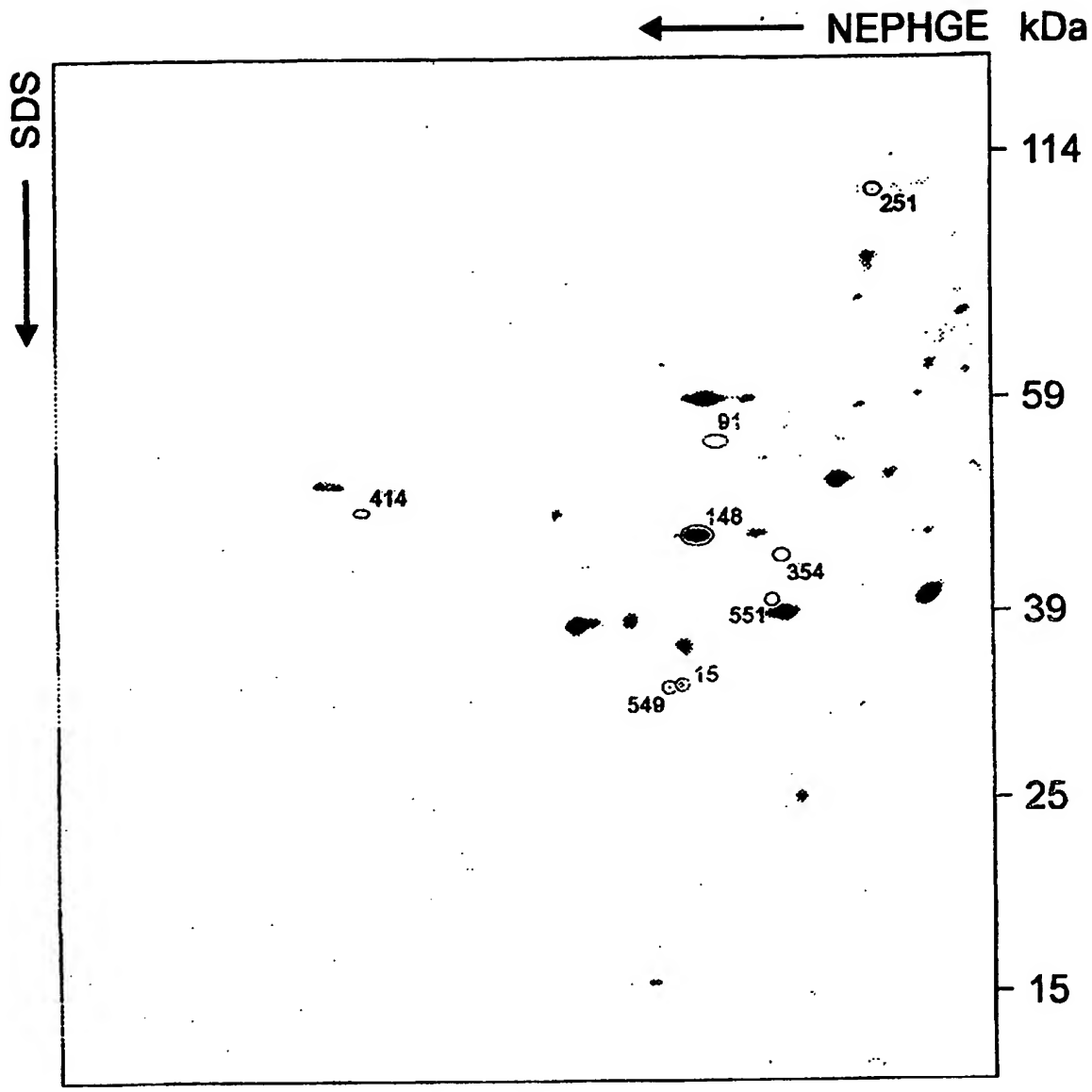


FIG. 4

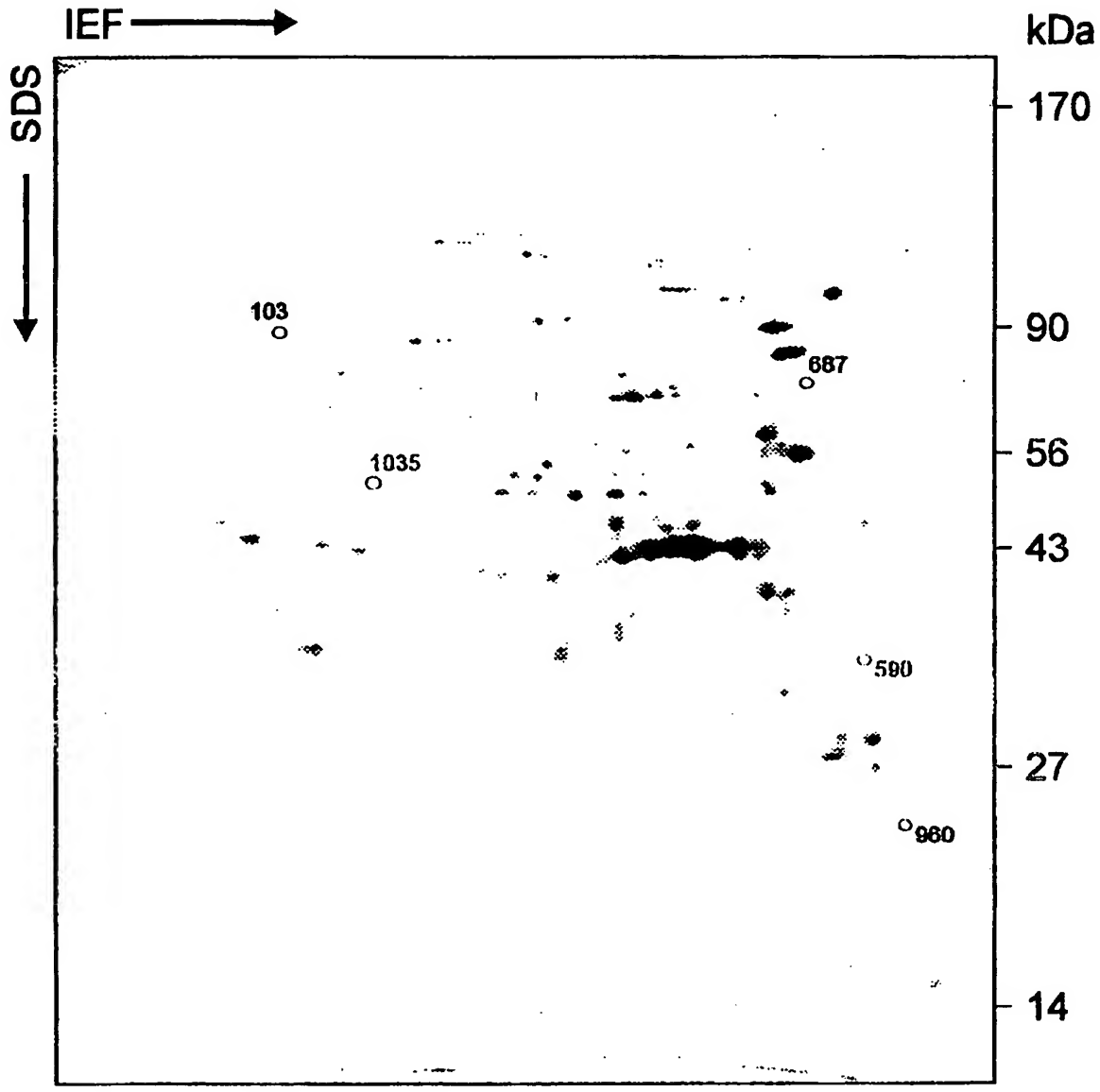


FIG. 5

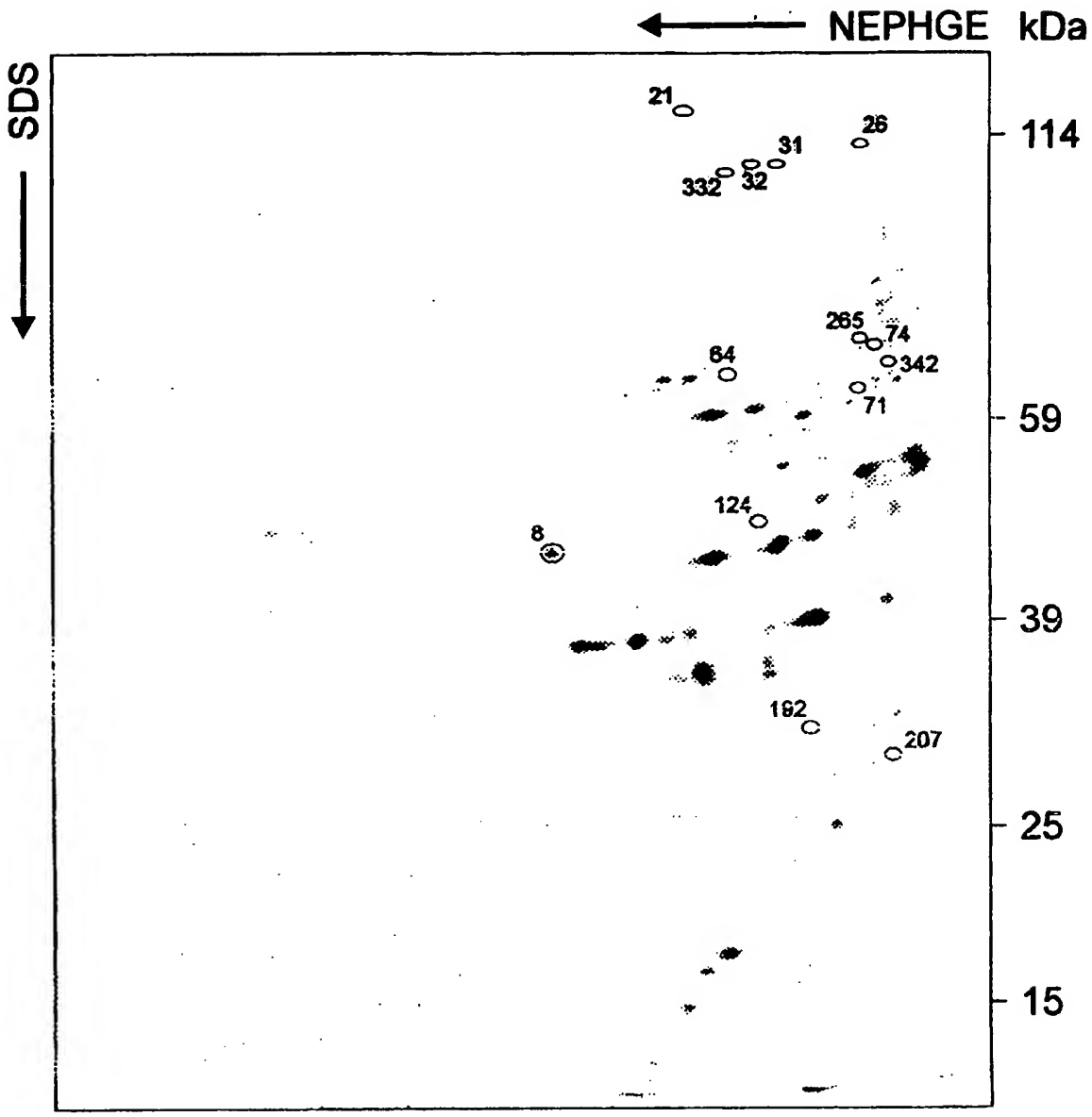
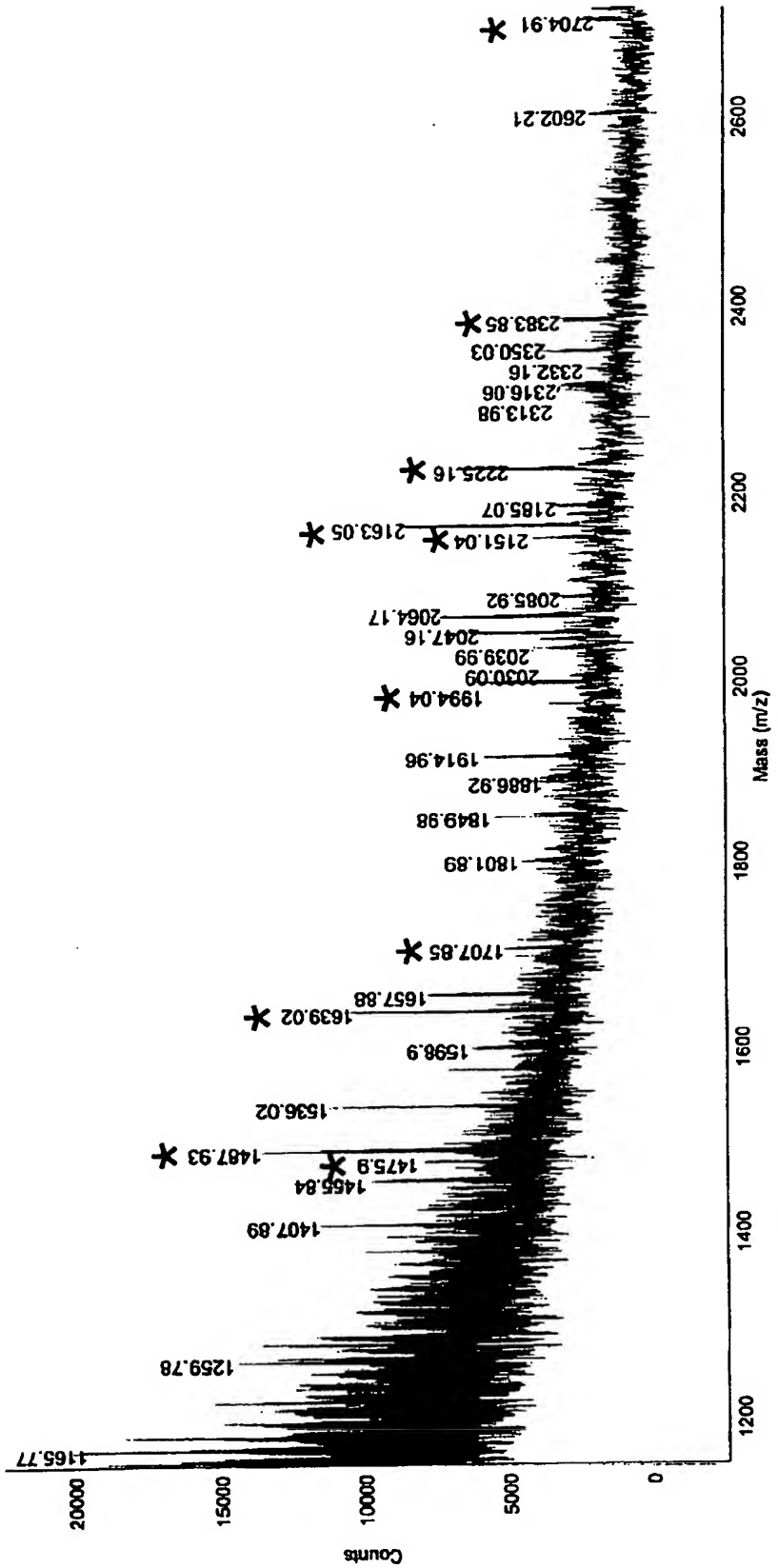

NEPHGE kDa
SDS
21
26
31
332
32
265
74
64
342
71
124
8
162
207
114
59
39
25
15

FIG. 6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20000
15000
10000
5000
0
Mass (m/z)
1200
1400
1600
1800
2000
2200
2400
2600
1165.77
1259.78
1407.89
1455.84
1475.9
1487.93
1536.02
1598.9
1639.02
1657.88
1707.85
1801.89
1849.98
1886.92
1914.96
1994.04
2030.09
2039.99
2047.16
2064.17
2085.92
2151.04
2163.05
2185.07
2225.16
2313.98
2316.06
2332.16
2350.03
2383.85
2602.21
2704.91

Fig 7

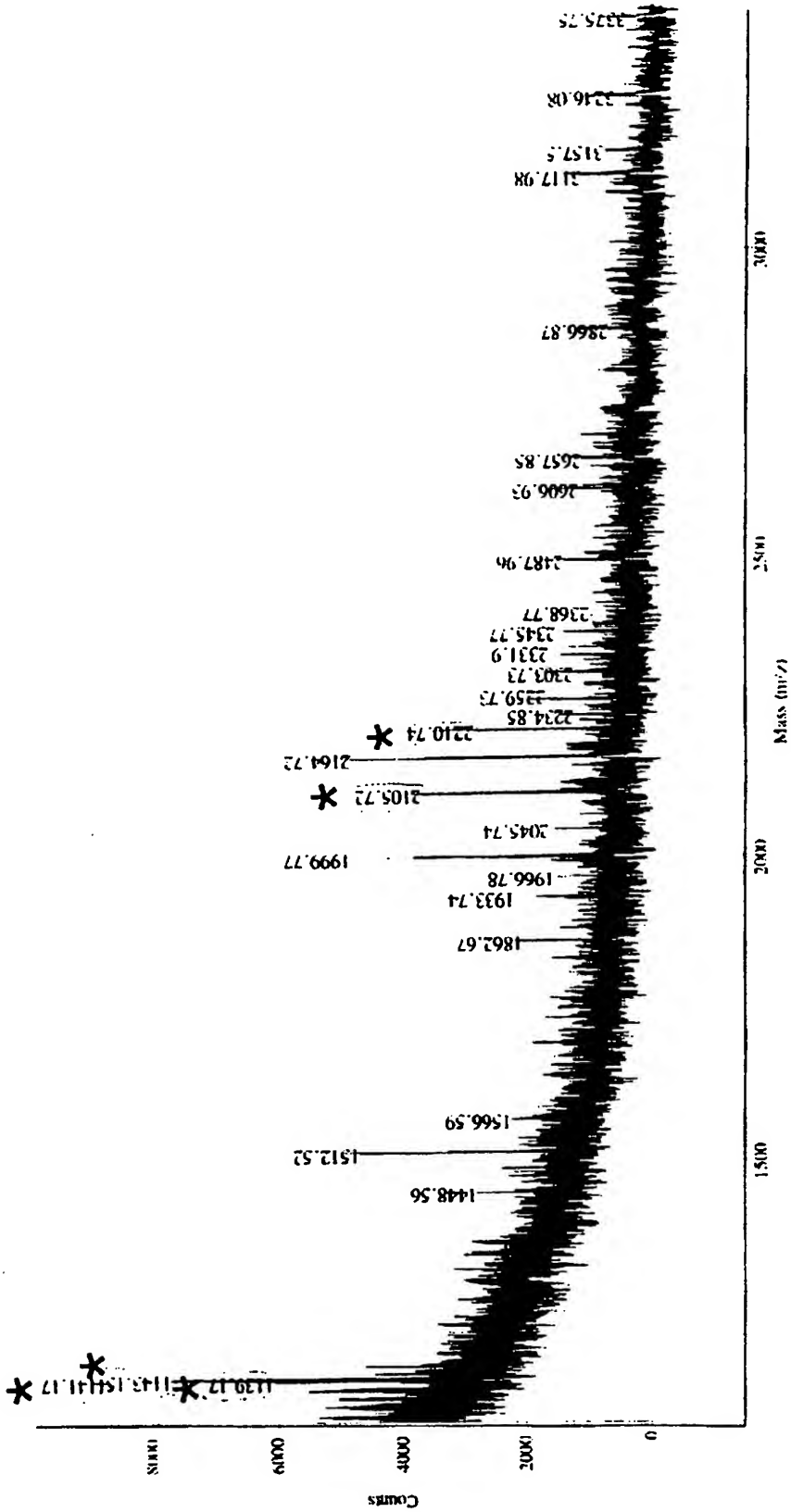
Counts
Mass (m/z)
1130.17
1143.15
1448.56
1512.52
1566.59
1862.67
1933.74
1966.78
1999.77
2045.74
2105.72
2164.72
2210.74
2234.85
2303.73
2331.9
2345.77
2368.77
2487.96
2606.93
2657.85
2866.87
3117.98
3157.5
3216.08
3325.75

Fig 8

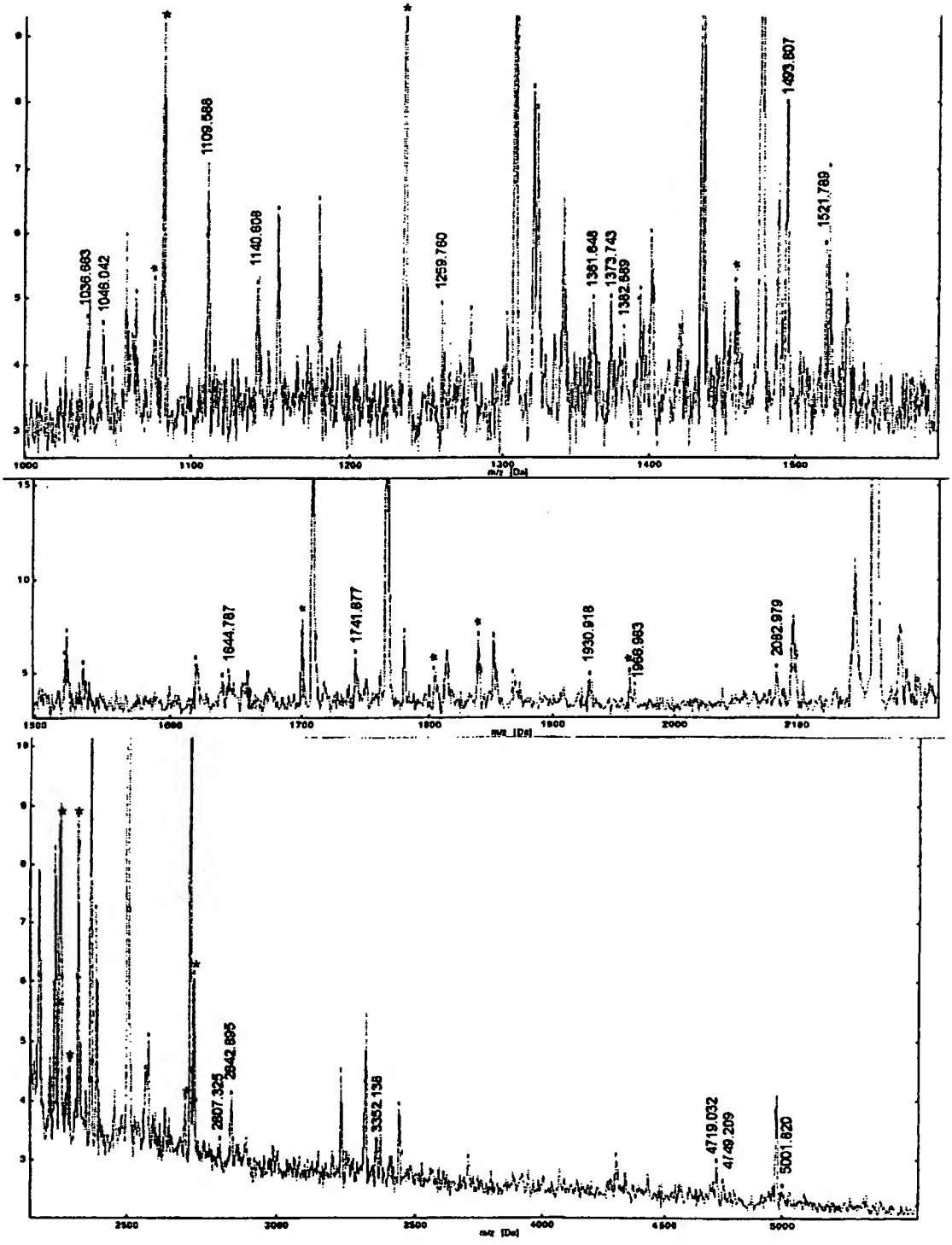
1038.663
1046.042
1109.588
1140.608
1259.760
1361.648
1373.743
1382.889
1493.807
1521.789
1644.787
1741.877
1930.918
1966.983
2082.979
2807.325
2842.695
3352.138
4719.032
4749.209
5001.820
m/z [Da]

FIG. 9

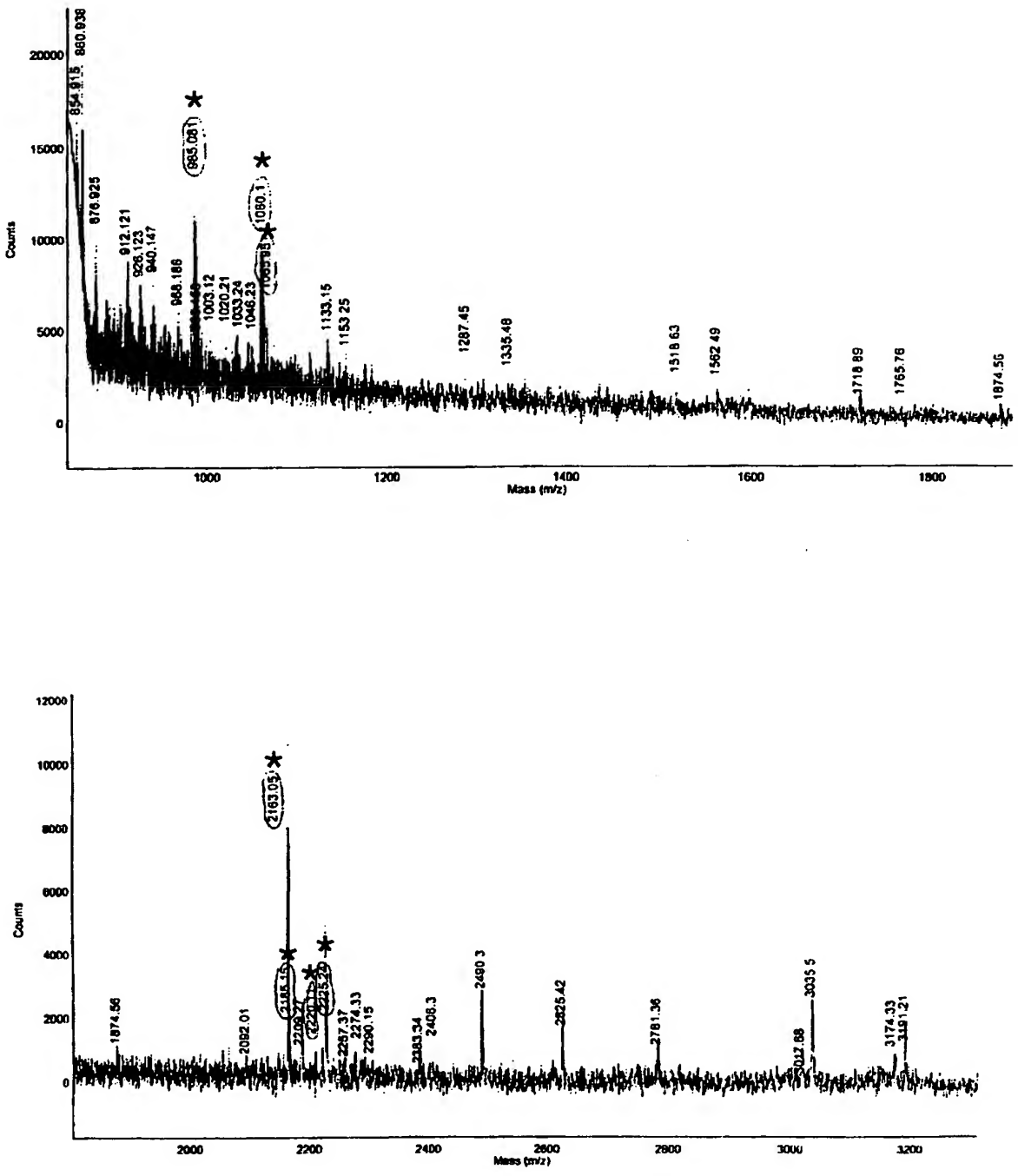
Counts
Mass (m/z)
965.061
1080.1
2163.05
1874.56
2082.01
2408.3
2490.3
2825.42
2781.36
3035.5
3174.33
3191.21

FIG. 10

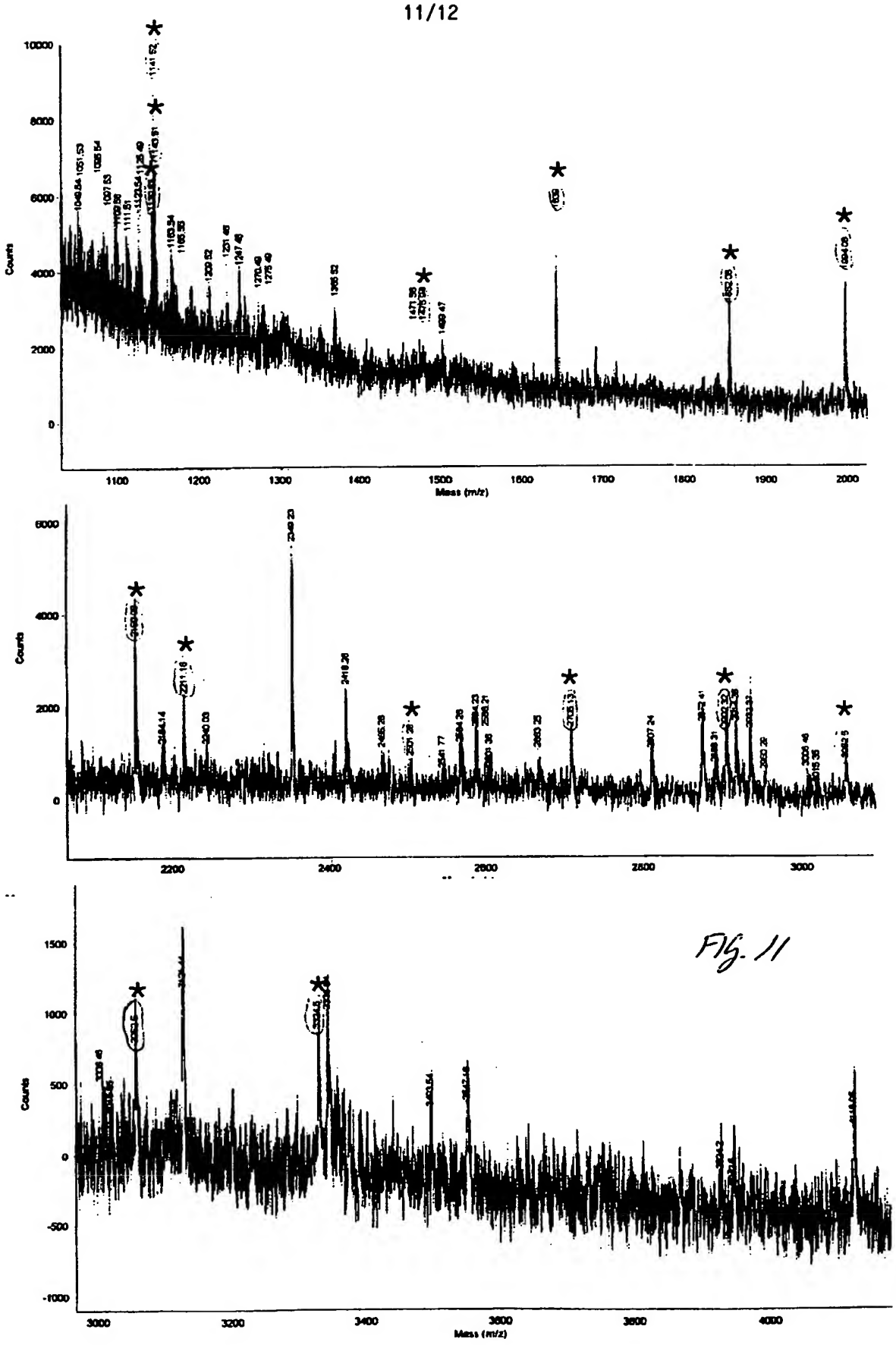

FIG. 11

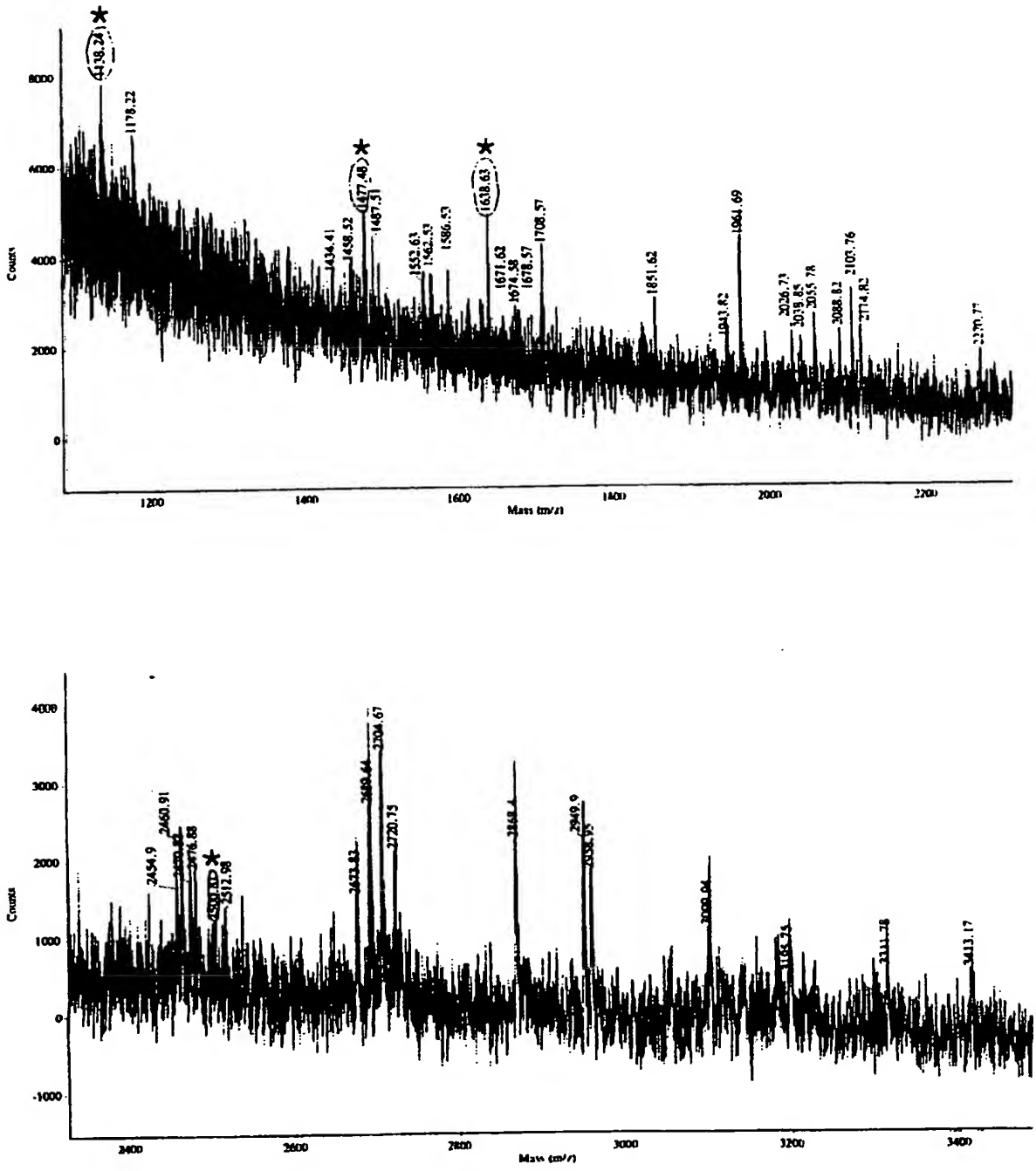
Counts
Mass (m/z)
1200
1400
1600
1800
2000
2200
2400
2600
2800
3000
3200
3400
4138.24
1178.22
1477.48
1487.51
1638.63
1708.57
1851.62
1964.69
2105.76
2454.9
2460.91
2512.98
2693.83
2704.67
2720.75
2858.4
2949.9
3000.04
3413.17

Fig. 12